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JUNE, 1950

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PROCEEDINGS

OF THE

CHEMICAL SOCIETY.

Minutes of a

SCIENTIFIC MEETING

held at the Royal Institution, Albemarle Street, London, W.1, on May 4th, 1950, at 7.15 p.m.

The President, PROFESSOR E. K. RIDEAL, M.B.E., M.A., D.Sc., F.R.S., was in the Chair.

MINUTES.

The Minutes of the Meeting held at Burlington House on March 16th, 1950, and of the Meeting held in the Zoology Department, King's Buildings, West Mains Road, Edinburgh, on March 30th, 1950, were read, and were confirmed and signed.

FORMAL ADMISSION OF FELLOWS.

The following were admitted Fellows of the Society: Betty H. M. London, F. J. Macrae, S. C. Snell, H. Tauber, D. R. Warren, Denys J. Voaden, Arthur D. Thomas, J. F. Cavalla, A. R. Pinder, J. E. Saxton.

TILDEN LECTURE.

The President called upon Professor F. S. Spring to deliver the Tilden Lecture entitled, "Recent Advances in the Chemistry of the Steroids." At the conclusion of the lecture, a vote of thanks to Professor Spring, proposed by Professor E. R. H. Jones, was carried with acclamation.

OFFICIAL ANNOUNCEMENTS.

DEATHS.

The Council regret to announce the deaths of the following Fellows:

	Elected.	Died.
Nathan Cohen (Manchester)	Feb. 6th, 1947.	Aug. 1949.
James Joseph Cowperthwaite (Salford)	Apr. 4th, 1946.	Dec. 15th, 1949.
Charles Stanley Gibson (Kingswood), S. 1924—33; V.P. 1933—36, 1942—45	May 2nd, 1907.	Mar. 24th, 1950.
Jeremy Hale (Harpenden)	May 7th, 1936.	Oct. 1948.
Sir (Walter) Norman Haworth (Birmingham), C. 1923—26, 1931—34; V.P. 1934—37, 1942—44, 1946—50; P. 1944—46	Feb. 18th, 1909.	Mar. 19th, 1950.
Eric Heymann (Carlton, Victoria)	June 15th, 1944.	Nov. 23rd, 1949.
Thomas McLean (Manchester)	June 19th, 1941.	Jan. 19th, 1950.
Frances Mary Gore Micklethwait (Gerrards Cross)	Dec. 2nd, 1920.	Mar. 25th, 1950.

CONGRATULATIONS.

The President has conveyed the congratulations of the Council to Mr. Harold Picton (Letchworth), who completed 60 years of Fellowship on April 17th, 1950, and to the following, who completed 50 years of Fellowship on May 3rd, 1950:

Sir (Arthur) Charles Davis (Cambridge).
Reginald Gordon Halstead (E.6).
James Herbert Haynes (Southwick).
James Henry Kershaw (Worthing).
Thomas Macara (N.8).

ELECTION OF NEW FELLOWS.

The following 117 candidates were elected Fellows of the Society on May 4th, 1950:

James Hunter Adam.
Lorenz Stephan Adler.
Raj Bahadur Agarwal.
Patrick Andrews.
Brian Baker.
Wolfgang Gerson Barb.
Anthony Kenneth Barbour.
Philip Henry Trim Beckett.
Henry Semple Blair.
Brian Keith Blenkinship.
Humphrey John Moule Bowen.
Milton Neil Brady.
George Michel Bristow.
Robert Stewart Brown.
Thomas Bryce.
Ronald Leno Bull.
Harold Theodore Byck.
Douglas John Carswell.
Anthony Clifford Caws.
William Henry Chapman.
John Martin Chemerda.
Roy Edward Cockaday.
Raymond Colledge.
Joseph Holgate Cooper.
John William Cornish.
Basil Stanley Cox.
Roger Alleyn Davison.
Timothy Leslie Dawson.
Norman Basil Dean.
Jean Hill Duffus.
Thomas Melanby Dunn.
Harry Derek Edwards.
James Ronald Eglen.
William David English.
John Edwin Falk.
Peter Eric Fielding.
Adam Hastings Fiske.
Walter Julius Freund.
Neil Robert Francis.
Ronald Frost.
Tejendra Nath Ghosh.
Ian Gordon Francis Gilbert.
Frank Philip Gloyns.
Irving Goodman.
Murray Alexander Mungo Graham.
Edward Joshua Greenhow.
Anil Kumar Gupta.
John Alwyn Hall.
John Panton Hall.
Elinor Margaret Hankins.
Frank Elias Harper.
Eric Frank Payne Harris.
Frederick Allan Harwood.
Robert Donald Hoskin Heard.
Henry Martin Hellman.
Francis Hewitt.
Esau Abbas Hoesin.
Archibald John Paton Hogg.
Milton Jones Hogsed.
Arthur Frederick LeCore Holding.
Joseph Gilbert Hooley.
Fridolin Alfonse Hoyer.
Michael Alexander Jermyn.
Victor Jones.
Frederick John Julietti.
Bernard Crook Kilkenny.
Ferdinand Hobert Kruse.
Richard Vincent Charles Kynch.
Patrick Joseph Leahy.
Colin Graham Macdonald.
John Finnie McGechen.
John Henry Mallows.
Michael Albert Manganelli.
Eric George Meek.
Peter Edward Molloy.
Sayyid Shah Muhammad.
Dennis Daniel Ernest Newman.
Henry Pannell.
Kenneth Richard Payne.
Raymond Dixon Peacock.
Ronald Sandison Pearce.
Michael Joseph Pryor.
Stanley Arthur Ray.
James Edgeley Fisher Renton.
Charles Bertram Robert Reynolds.
David Samuel Petrie Roebuck.
Roy Alan Russell.
Dilwyn Morgan Samuel.
Seymour Schmukler.
Henry Joseph Schneider.
Mahadeva Lal Schroff.
Joseph R. Schwartz.
Anthony Walter Scopes.
Alastair Ian Scott.
Kurt Lothar Seligman.
Edward Shotton.
James Noel Sibson.
Derrick John Silver.
Robert Charles Morris Smith.
Lumir Sommer.
Peter Adrian Hugh Sperring.
Francis Sydney Statham.
John Bedford Stenlake.
Edward Robertson Stuart.
William Arthur Swindin.
Walter Charles Taylor.
Joseph Knight Thompson.
Eric Vernon Truter.
Richard Joseph Tudor.
Roy Stewart Varley.
Hans Max Wagner.
William Derek Walsh.
Denman George Wibberley.
Roger Michael Williamson.
John Barrett Wilton.
Robert William Woodhead.
Walter Bruce Yeoman.

CORDAY-MORGAN MEDAL AND PRIZE.

The illustration opposite shows the Corday–Morgan Medal designed for the Society by Mr. Percy Metcalfe, C.V.O. The portrait of Sir Gilbert Morgan on the obverse is intended to represent his interests, which covered both Pure and Applied Chemistry. The

The Corday-Morgan Medal.

[*To face Proceedings, p. 78.*

reverse of the medal depicts a Mediterranean land-crab to symbolise the chelate compounds ($\chi\eta\lambda\acute{\eta}$ = a crab's claw), which will always be closely associated with the name of Sir Gilbert Morgan (cf. Morgan and Drew, *J.*, 1920, **117**, 1457).

Applications for the Medal and Prize for 1949 must be received not later than December 31st, 1950. Applications in respect of the award for 1950 are due before the end of 1951. The rules governing the award were last published in the *Proceedings* for April 1950.

A selection committee, with the President as Chairman, and consisting of the immediate Past-President and the six Vice-Presidents who have not filled the office of President, has been appointed to submit to Council recommendations for the award of the Medal and Prize.

ANNUAL SUBSCRIPTIONS UNDER COVENANT.

Fellows who pay United Kingdom Income Tax at the full rate on any part of their income can substantially benefit the Society without any cost to themselves by covenanting to subscribe regularly for seven years.

By virtue of its status as a Charity, the Society is able to reclaim the tax paid by a Fellow on the amount of the annual subscription if that subscription is paid under Covenant.

For example, if a Fellow who at present pays an annual subscription of £3 10*s.* undertakes to pay this sum annually for seven years the Society is able to recover from Inland Revenue £2 17*s.* 3*d.* which has been paid as Income Tax. Similarly, Fellows who regularly receive a wider range of publications than are available under the basic subscription may covenant for a correspondingly larger sum. It should, however, be noted that there can be no reduction in the net amount due annually from those Fellows who subscribe under covenant, since the tax is refunded for the benefit of the Society as a whole and not for the benefit of individual Fellows. Full details of this arrangement will be circulated to Fellows individually in due course. The Council invites Fellows to assist the Society in this way by completing a Deed of Covenant.

Several hundreds of Fellows already pay their subscriptions by Bankers' Order. By signing a Covenant and without disturbing the present arrangement with their banks, such Fellows (if paying Income Tax at the Full Rate) could substantially increase the Society's income.

Those who are able to claim that Fellowship of the Society is a condition of their employment or a necessary expense of their business, and so obtain relief from taxation on the amount of their subscription, should not complete a Deed unless they are prepared to forego tax relief in future years. Those who do not obtain such relief at present and decide to complete a covenant will not be prevented, if their circumstances should change, from obtaining tax relief at a later date.

The Covenant may also be used by Life Fellows or by any others who might wish to contribute to the general Funds of the Society.

Those who sign Covenants will be asked later to give the Society each year, a certificate that Income Tax has been paid. The Society will supply the necessary simple form at the appropriate time.

SCIENTIFIC MEETINGS 1950—51.

The following dates for Scientific Meetings during the session 1950—51 have been approved by Council:

1950.	1951.
October 12th.	January 18th.
,, 26th.	February 1st.
November 16th.	,, 15th.
December 14th.	March 15th.
	,, 20/21st.*
	May 3rd.
	June 7th.

* Anniversary Meetings, to be held in London.

The Council have also agreed that the time of evening meetings should be changed from 7.15 to 7.30 p.m.

CENTENARY LECTURERS.

Dr. K. Linderström-Lang and Professor R. B. Woodward have been appointed Centenary Lecturers for the session 1950—51.

VACANCIES ON COUNCIL 1950—51.

Vice-Presidents who have filled the Office of President.

Professor N. V. Sidgwick, who was due to retire at the Annual General Meeting in March 1950, remains a Vice-President in place of the late Sir Norman Haworth.

Constituency III—North West England, North Wales and Isle of Man.

The Council have unanimously co-opted Dr. G. Baddeley as a Member of Council until the Annual General Meeting in 1951 to fill the vacancy caused by the death of Dr. A. E. Gillam.

MEETING OF COUNCIL.

A Meeting of Council was held on May 4th, 1950.

The Council stood as a tribute to the memory of Professor C. S. Gibson, a former Honorary Secretary and Vice-President of the Society, and of Sir Norman Haworth, a Past-President, whose deaths were reported.

The Report of the meeting of the Publication Committee held on March 16th, 1950, was received, and it was agreed that a statement assembling new decisions of nomenclature taken during the year should be published annually in the December issue of the *Journal*.

The Council received with pleasure an invitation to hold the Anniversary Meetings for 1952 in Dublin, and accepted provisionally.

The Report of the Meeting of the Joint Library Committee held on March 22nd, 1950, was received, and the list of books recommended for purchase was approved.

It was agreed not to make any change in the prices of publications to be charged in 1951.

It was reported that, arising from the increased cost of raw materials brought about by the devaluation of sterling, the price of paper had been increased, and that, on the basis of present consumption, the additional cost to the Society would be about £750 per annum.

The thanks of the Council have been conveyed to Miss N. J. Broadway, Dr. J. S. Lumsden, Mr. A. P. Mieras, and Mr. G. S. Ward for gifts of the Society's publications.

The Report of the meeting of Local Representatives held on March 30th, 1950, was adopted.

The resignations of Dr. F. R. Goss (Leeds) and Dr. J. D. M. Ross (St. Andrews and Dundee) as Local Representatives were accepted with regret, and Mr. P. A. Briscoe and Dr. H. T. Openshaw were appointed.

Professor D. H. Hey and Sir John Simonsen were nominated to serve on the British National Committee for Chemistry and the Council of Management of the Lawes Agricultural Trust, respectively, in the place of the late Sir Norman Haworth, who had represented the Society on both Committees.

Professor D. H. Hey and Professor H. Burton were appointed to represent the Society at the celebrations of the 50th Anniversary of the Discovery of the Grignard Reagents in Lyons on May 13th, 1950.

It was reported that Professor F. A. Paneth has accepted an invitation to represent the Society at the Celebrations of the 50th Anniversary of the Discovery of Radium to be held in Paris on July 16th to 20th, 1950.

THE LIBRARY.

From July 17th to September 30th, the Library will be open from 10 a.m. to 5 p.m. daily, except during the fortnight, August 7th to 19th, 1950, inclusive, when it will be closed for revision and cleaning.

METALLURGICAL APPLICATIONS OF THE ELECTRON MICROSCOPE.

Papers presented at a Symposium held in London on November 16th, 1949, by the Institute of Metals in association with the Chemical Society, the Faraday Society, the Institute of Physics, the Institution of Electrical Engineers, the Iron and Steel Institute, the Physical Society, and the Royal Microscopical Society have now been published by the Institute of Metals, 4 Grosvenor Gardens, S.W.1., as a Monograph (price to non-Members of the Institute of Metals 21*s.* post free).

Some of the papers are of a review character and summarize the work that has been done so far in Great Britain, France, Germany, and the United States; others record research results hitherto unpublished.

The Symposium was attended by about 300 scientists from various countries. The discussion, which is fully reported in the Monograph, contains important contributions from metallurgists and from leading workers in the field of electron microscopy. The Monograph as a whole forms, therefore, a comprehensive and up-to-date guide to the use of the electron microscope in metallurgy.

MEETINGS OUTSIDE LONDON.

SHEFFIELD.

Tilden Lecture, "Recent Advances in the Chemistry of the Steroids," by Professor F. S. Spring, D.Sc., F.R.I.C.

A joint meeting with the University Chemical Society was held in the Chemistry Lecture Theatre of the University on April 27th, 1950, with Professor R. D. Haworth in the Chair.

In his lecture, which was also given in London on May 4th, Professor Spring dealt with cortisone and related compounds.

On the motion of Dr. T. S. Stevens, a cordial vote of thanks was given to the Lecturer.

SOUTHAMPTON.

"Trace Elements in Plant Life," by Dr. W. A. Roach, A.R.I.C.

A joint meeting with the Royal Institute of Chemistry (Mid-Southern Counties Section) and the Portsmouth and District Chemical Society was held at the Municipal College, Portsmouth, on April 26th, 1950, with Mr. R. Chatterton in the Chair.

After outlining the nature of the trace elements and the methods by which they are determined, Dr. Roach went on to show how deficiency of these elements is detected and the various methods by which the deficiencies can be remedied on the large scale. His lecture was illustrated by a number of slides showing the equipment employed, and the results obtained, and also by a number of incidents drawn from his wide and varied experience in field and plantation, both in this country and abroad.

A number of those present participated in the ensuing discussion and the meeting terminated with a hearty vote of thanks proposed by Dr. C. G. Lyons, and carried with acclamation.

"Recent Synthetical Developments in Pyrethrum Chemistry," by Dr. S. H. Harper.

A joint meeting with the University College Chemical Society was held in the Physics Department of University College, Southampton, on May 5th, 1950, with Dr. A. R. Burkin in the Chair.

After a brief description of pyrethrum cultivation, Dr. Harper discussed the nature and structure of the active principles of the plant and then dealt with recent studies which have resulted in the synthesis of portions of pyrethrin molecules and related substances. The lecture was illustrated by excellent slides showing synthetical routes.

A discussion followed, and a vote of thanks to Dr. Harper, proposed by Dr. I. G. M. Campbell, was warmly accorded.

LIST OF APPLICATIONS FOR FELLOWSHIP

(Fellows wishing to lodge objections to the election of these candidates should communicate with the Honorary Secretaries within ten days of the date of publication of the Journal *for June,* 1950. *Such objections will be treated as confidential. The forms of application are available in the Library.)*

***Addicott, Harold Frank Simpson.** British. 13, Shrewsbury Lane, Shooters Hill, S.E.18. Student at Woolwich Polytechnic. *Signed by:* G. H. Jeffery, A. E. Akerman, J. Leicester.

Allsop, Harry. British. Brown, Bayley's Steel Works Ltd., Leeds Road, Sheffield, 9. Chief metallurgist. *Signed by:* G. Larkin, W. E. Ballard, R. Belcher.

***Barnes, Geoffrey Thomas.** British. Wesley College, Newtown, N.S.W., Australia. Research Student. *Signed by:* R. J. W. Le Fèvre, T. Iredale, L. E. Lyons.

***Beck, Cyril Arthur.** British. 18B, Wild Street Estate, Kingsway, W.C.2. Student at Woolwich Polytechnic. *Signed by:* A. I. Vogel, L. Ellison, J. Leicester.

***Clist, Brian George.** British. Mountshayne, Hemyock, Nr. Cullompton, Devon. Student. *Signed by:* J. K. N. Jones, F. H. Pollard, L. Hough.

***Conan, Henry Robert,** B.A. and B.Sc. (Oxon.). British. 26, Waterloo Road, Dublin. Technical assistant at W. & H. M. Goulding, Ltd., Dublin. *Signed by:* J. W. Parkes, A. G. G. Leonard, T. S. Wheeler.

Darwent, Basil de Bakerville, B.Sc. and Ph.D. (McGill). British. National Research Council, Ottawa, Ontario, Canada. Associate Research Chemist. *Signed by:* E. W. R. Steacie, G. W. Meadows, P. Agius.

De Mayo, Paul, B.Sc. (Lond.), A.R.I.C. British. 30, Mount Park Road, Ealing, W.5. Research Chemist, Department of Clinical Pathology, University College Hospital. *Signed by:* D. E. Ames, R. E. Bowman, W. Rigby.

Dewey, William Charles. British. 23, Northwood Road, Carshalton. Bacteriologist at The Counties Public Health Laboratories, S.W.1. *Signed by:* J. E. Coppock, R. L. Hoather, G. Miles.

***Felton, Edward Walter,** B.Sc. (Manc.), A.R.I.C. British. 10, Miller Road, Oldham. Chemist. *Signed by:* T. G. Halsall, G. N. Burkhardt, C. Binns.

Fogg, Alan, M.A. and B.Sc. (Oxon.), A.R.I.C. British. 69, Court Lane, Dulwich, S.E.21. Industrial Consultant. *Signed by:* A. W. Marsden, S. J. Rowland, A. G. Pollard.

***Frith, William Cyril,** B.Sc. (Manc.). British. 39, Bridge Mont, Whaley Bridge, Nr. Stockport. Research Student at Manchester University. *Signed by:* F. Fairbrother, T. H. H. Quibell, S. Dunstan.

Green, Dennis Mario, B.Sc. (Lond.), A.R.I.C. British. 134, Malvern Road, West Kilburn, N.W.6. Civil Servant. *Signed by:* H. J. Dothie, N. W. Squance, P. J. Hardwick.

Harrigan, Francis Patrick, B.Sc. (Glas.). British. C/o Glaxo Laboratories, Ltd., Greenford. Development Chemist. *Signed by:* H. W. Gurney, A. Jackson, A. P. Best.

***Havard, David Colin.** British. 159, Ealing Road, Wembley. Student at Acton Technical College. *Signed by:* J. H. Skellon, G. J. L. Griffin, J. W. Spence.

***Horlock, Anthony Barrington,** B.Sc. (Lond.), A.R.I.C. British. 1A, Bridle Road, Shirley, Croydon. Chemist. *Signed by:* E. C. Allison, J. R. Miller, R. E. Dabby.

***Kay, Isobel Ann,** B.Sc. (Lond.). British. 50, Spencer Road, Twickenham. Research Chemist. *Signed by:* V. A. Petrow, O. Stephenson, J. S. Webb.

Lewis, Graham Ethelbert, B.Sc. (Adelaide). Australian. 11, Princes Street, Croydon, South Australia. Research Student. *Signed by:* G. M. Badger, R. Pettit, J. S. Shannon.

Loughlin, Rev. Wilfrid James, B.Sc. and Ph.D. (L'pool.), A.R.I.C. British. Ampleforth College, York. R.C. Priest, Engineer and Estate Manager at Ampleforth College. *Signed by:* R. J. S. Beer, W. B. Whalley, G. W. K. Cavill.

***Lunt, John Cooper,** B.Sc. (Lond.), A.R.C.S. British. 21, Palace Gate, Kensington, W.8. Research Student. *Signed by:* B. C. L. Weedon, J. A. Elvidge, R. P. Linstead.

May, Charles Gerard, M.Sc. (Manc.). British. 26, Bradford Avenue, Great Lever, Bolton. Research Student at Manchester University. *Signed by:* H. D. Springall, G. N. Burkhardt, T. H. H. Quibell.

***McDonald, Gerald William Goddard,** B.Sc. (Glas.). British. La Carriere, Pointe-a-Pierre, Trinidad, B.W.I. Chemist. *Signed by:* J. W. Cook, J. Bell, T. H. Goodwin.

Meier, Richard Louis, B.Sc. (Illinois), M.A. and Ph.D. (Calif.). American. 24, Brundretts Road, Manchester, 21. Fulbright Research Fellow at Manchester University. *Signed by:* K. F. Coles, I. Goodman, E. I. Borrows.

Mullen, Bernard Francis. Irish. Oriel, North Road, Drogheda, Ireland. Chief Chemist at Drogheda Chemical Manure Co. Ltd. *Signed by:* T. S. Wheeler, D. O'Tuama, J. G. Belton.

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(List of papers received between April 21st and May 17th, 1950.)

"Deoxyribonucleosides and related compounds. Part II. A proof of the furanose structure of the natural 2-deoxyribonucleosides." By D. M. Brown and B. Lythgoe.

"Experiments on the synthesis of purine nucleosides. Part XXVII. 1 : 2 : 3 : 5-Tetra-acetyl D-xylofuranose and the D-xylofuranosides of theophylline and adenine." By P. Chang and B. Lythgoe.

"Reactions of organic peroxides. Part II. Reactions of *iso*propylbenzene hydroperoxide." By E. G. E. Hawkins.

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"A theoretical treatment of the Diels–Alder reaction. Part II. Polyenes, arylpolyenes, and related molecules." By R. D. Brown.

"Reaction of diacetyl with ethyl orthoformate." By D. A. Harris.

"Deoxy-sugars. Part XIII. Some observations on the Feulgen nucleal reaction." By W. G. Overend.

"Some reactions of *p*-tolyl toluene-*p*-thiolsulphonate." By H. T. Hookway.

"The fluorination of organic compounds containing nitrogen." By R. N. Haszeldine.

"Selective oxidations with red lead." By L. Vargha and M. Reményi.

" Steroids and related compounds. Part IX." By B. ELLIS and V. PETROW.
" The preparation of aluminium trilaurate, and the absence of gelling of the compound in hydrocarbons." By J. GLAZER, T. S. MCROBERTS, and J. H. SCHULMAN.
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" The absorption of quinine by a carboxylic acid ion-exchange resin." By L. SAUNDERS and R. SRIVASTAVA.
" The Franck–Condon principle and the size of the excited benzene molecule." By D. P. CRAIG.
" Esters containing boron and selenium." By H. G. COOK. J. D. ILETT, B. C. SAUNDERS, and G. J. STACEY.
" Studies on phosphorylation. Part VI. The reaction between organic bases and esters of the oxy-acids of phosphorus. An interpretation based on a comparison of certain aspects of the chemistry of sulphur and phosphorus." By V. M. CLARK and A. R. TODD.
" Studies on phosphorylation. Part VII. The action of salts on neutral benzyl esters of the oxy-acids of phosphorus. A new method of selective debenzylation." By V. M. CLARK and A. R. TODD.
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" The anomalous reactions of Grignard reagents." By H. J. SHINE.
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(b) *Miscellaneous*

CANADA, DOMINION OF. *National Research Council. Division of Applied Biology.* Quarterly Report. Vol. I, etc. Ottawa 1949 +. (*Reference.*) From the Council.

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GORTNER, R. A. Outlines of biochemistry. 3rd edition. Edited by R. A. GORTNER, jun., and W. A. GORTNER. New York 1949. pp.

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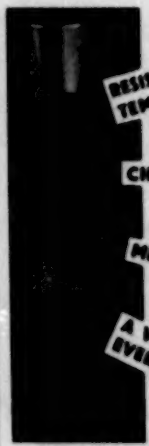

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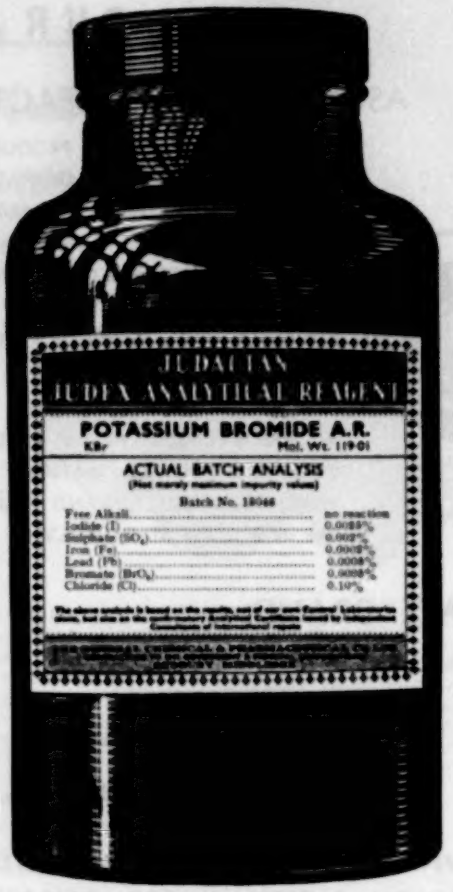

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Whittle, E. See Evans, M. G., **1524.**
Whyte, D. R. A. See Cocker, W., **1519.**
Wiggins, L. F., and Wood, D. J. C., **1566**
Wood, D. J. C. See Wiggins, L. F., **1566**
Young, E. H. P. See Hoggarth, E., **1582.**
Youngson, G. W., and Melville, H. W., **1613.**

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292. *The Stereochemistry of Catalytic Hydrogenation. Part VIII.* Pyrolysis of the Six Perhydrodiphenic Acids. Limitations of the Blanc Rule.*

By Selby B. Davis, W. E. Doering, Philip Levine, and R. P. Linstead.

All six of the stereoisomeric perhydrodiphenic acids give pyroketones (perhydrofluorenones). The three acids of the *syn*-series give the same mixture of *syn*-ketones, and the three *anti*-acids give the same *anti*-ketone mixture. The bearing of this on work on steroid oxidation products is discussed.

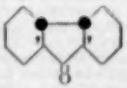
When ring B of the steroid skeleton is opened, dibasic acids can be obtained which are of the perhydrodiphenic acid type. Although 1 : 6-dicarboxylic acids, some compounds of this class have failed to give pyroketones under Blanc's conditions (*Compt. rend.*, 1907, **144**, 1356) or under similar experimental treatment. This anomaly at one time led to the erroneous formulation of ring B as five-membered (Windaus and Dalmer, *Ber.*, 1919, **52**, 162; Wieland and Weyland, *Z. physiol. Chem.*, 1920, **110**, 123). Later, when it became clear for other reasons that the ring was six-membered, Wieland and Dane (*ibid.*, 1932, **210**, 268) suggested that the rule that adipic acids give pyroketones was limited to acyclic and monocyclic acids and failed with perhydrodiphenic acids. Ruzicka (*Helv. Chim. Acta*, 1933, **16**, 216) expressed the view that the steroid perhydrodiphenic acids failed to give ketones because they contained at least one *trans*-linkage.

Investigations of the model compounds, the perhydrodiphenic acids themselves, have been made by Vocke (*Annalen*, 1934, **508**, 1), Hückel (addendum to Vocke's paper), and Linstead and Walpole (*J.*, 1939, 850).

The interpretation of this early work was somewhat complicated by the incorrect assignment of the perhydrodiphenic structure to two acids. We refer to this matter later. However, the subject has been placed on a firm basis by the isolation and interrelation of all six stereoisomeric forms of perhydrodiphenic acid (Linstead and Doering, *J. Amer. Chem. Soc.*, 1942, **64**, 1991), and against this background it is possible to summarise the early results. Three isomeric acids are relevant, those of m. p. 244° (now 247°), 273° (now 289°), and 220° (now 223°), described by Vocke, Hückel, and Linstead and Walpole, respectively. We now know all these to be perhydrodiphenic acids with the configurations. *trans-anti-trans*, *cis-syn-cis*, and *trans-syn-trans* respectively. All give pyroketones.

The isolation of the remainder of the possible stereoisomeric forms of the acid and the proof of their configuration (Linstead and Doering, *loc. cit.*; Linstead, Davis, and Whetstone, *ibid.*, p. 2009; Davis and Linstead, following paper) have enabled us to complete the investigation.

We can now report that all six acids readily yield pyroketones. The same ketonic product is obtained from the three acids of the *syn*-series: *cis-syn-cis* (m. p. 289°), *cis-syn-trans* (m. p. 200°), and *trans-syn-trans* (m. p. 223°). It is, not unexpectedly, a mixture of two (perhaps three) of the possible *syn*-ketones (I), *i.e. cis-cis*, *cis-trans*, or *trans-trans*. It gives a mixture of oximes and a semicarbazone which is difficult to obtain homogeneous. The oximes are sensitive to light and heat. Careful crystallisation of the original mixture in a dark room gives a homogeneous *syn*-oxime, m. p. 173°, already isolated by Hückel (*loc. cit.*), but when this is heated or left in daylight, either in the solid state or in solution, the melting point falls and from the product a second *form*, m. p. 152—154°, can be isolated by crystallisation. This

(I.)  (II.)

change is very likely caused by an inversion of configuration of the ring involving hydrogen migration from a bridgehead, but *cis-trans* isomerism about the carbon–nitrogen double bond cannot be excluded.

* The experimental work described in this paper and the two succeeding Parts was carried out at Harvard University mainly in 1941. Publication has been greatly delayed from a variety of causes. The paper does not deal directly with the topic of catalytic hydrogenation. Nevertheless it seems best to add it to this series as it is concerned with the same compounds. R. P. L.

The three acids of the *anti*-series (*cis-anti-cis*, m. p. 198°; *cis-anti-trans*, m. p. 206°; *trans-anti-trans*, m. p. 247°) all give the same mixture of *anti*-perhydrofluorenones (II), characterised by the formation of the semicarbazone, already prepared by Vocke, and by Linstead and Walpole.

These ketonisations thus proceed in the expected way; there is an inversion of configuration at the α- but not at the β-carbon atom. The inversion may precede ketonisation for it has been shown that the acids of the *syn*-series are labile to heat. Thus the acid recovered (as anhydride) from the pyrolysis of both the *cis-syn-cis*- and the *cis-syn-trans*-isomerides was largely the *trans-syn-trans*-form. When either the *cis-syn-cis*- or the *trans-syn-trans*-acid was heated in an inert solvent at 243° there was formed a mixture mainly consisting of *trans-syn-trans*- with a small amount of *cis-syn-trans*-acid. The occurrence and the direction of these changes are fully as expected and fall into line with previous work on the relative stability of the *syn*-acids to reagents.

Although therefore the six authentic perhydrodiphenic acids all yield pyroketones, two other acids which have previously been assigned this constitution do not. These are the acid, m. p. 203°, of Linstead and Walpole (*loc. cit.*) and that, m. p. 213°, reported by Vocke (*loc. cit.*). Neither of these can be a perhydrodiphenic acid and their behaviour on pyrolysis is therefore not material to the present paper. Their probable constitutions have been discussed by Linstead and Doering (*loc. cit.*).

To revert to the central point of this work: As all the configurational forms of perhydrodiphenic acid give pyroketones, the abnormality of the steroid oxidation products is not caused by their being perhydrodiphenic acids, as suggested by Wieland, or by their having a *trans*-link, as proposed by Ruzicka. We think it probable that the difference between the perhydrodiphenic and the bilianic acids is one of degree and not of kind, and that the failure of the steroid acids to ketonise was caused by insufficiently drastic experimental conditions. It is well known that there is a good deal of variation in the conditions, particularly the temperature, under which different adipic acids yield ketones. For examples, it has been shown by Stange (*Z. physiol. Chem.*, 1933, **218**, 74) that an acid of this type which failed to cyclise under Blanc's conditions gave a pyroketone when its barium salt was heated to 390°.*

The conditions under which the perhydrodiphenic acids give ketones are described in the Experimental section. In no case was drastic treatment necessary, pyrolysis of the acid or anhydride at 310° or less being sufficient.

Experimental.

cis-syn-cis-Acid (compare Hückel, Linstead, and Walpole, *loc. cit.*).—The acid (m. p. 288—289°; 500 mg.) was heated for 2 hours at about 310° in a stream of dry nitrogen. The nearly colourless product was extracted with ether. From this solution aqueous sodium hydroxide extracted 50 mg. of a mixture of acids. The residue from the ether was then freed from anhydride by boiling 10% aqueous sodium hydroxide. This alkaline extract on fractional acidification (Linstead and Doering, *loc. cit.*) yielded 20 mg. of fairly pure *trans-syn-trans*-acid. The neutral ketonic fraction (150 mg.) was converted into the oxime (120 mg.) in the usual way. In a larger preparative experiment, the yield of mixed oxime was 5·01 g. from 8·65 g. of acid (78%).

The ketone was also prepared by heating the dry sodium salt of the *cis-syn-cis*-acid with acetic anhydride (Perkin and Thorpe, *J.*, 1904, **85**, 128). The carbon dioxide was swept out with dry nitrogen and weighed. Most was evolved between 130° and 140°. The yield of oxime was 1·36 g. from 5·43 g. of sodium salt. A similar mixture of oximes was obtained by both methods, melting mainly in the range 145—150°.

To obtain the pure oxime (needles, m. p. 172·5—174°) described by Hückel 8 crystallisations from 95% alcohol in a darkened room were necessary. The m. p. of this material fell when it was kept dry or in solution, particularly in light. A similar change was effected more quickly by heating the oxime or by treating it with sodium ethoxide. Crystallisations had to be carried out rapidly.

Oxime melting in the range 160—170° was kept for some weeks and then hydrolysed and the ketone reconverted into the oxime. Careful crystallisation from light petroleum yielded a second *syn*-perhydrofluorenone oxime, m. p. 152·5—154·5°, which appeared to be nearly homogeneous.

rac.-*cis-syn-trans-Acid*.—This acid (m. p. 198—200°; 250 mg.) was heated in nitrogen for 1 hour at 310°. The product was separated as described above into free acid (15 mg.), anhydride (yielding 10 mg. of an acid (mainly *trans-syn-trans*), and ketone (120 mg.). The ketone gave 100 mg. of a mixture of oximes, m. p. (crude) about 140—150°. Two crystallisations from methanol gave fine needles, m. p. 159—164°, which did not depress the m. p. of the oxime of similar m. p. prepared from the *cis-syn-cis*-acid. It was also indistinguishable from oxime prepared from *laevo-cis-syn-trans*-acid (see following paper).

* Aliphatic acids not containing an α-hydrogen atom fail to yield a pyroketone. This seems a fundamental property, connected with the mechanism of the reaction (see Neunhoeffer and Paschke, *Ber.*, 1939, **72**, 919).

The semicarbazone of the *syn*-series (m. p. 200—202°) is less easily formed than the oxime.

Thermal Inversion of syn-*Acids.*—(i) *cis-syn-cis*-Perhydrodiphenic acid (1 g.) was boiled under reflux for 2 hours in 1-methylnaphthalene (5 c.c.). The product was freed from a little unchanged *cis-cis*-acid by extraction with ether and dissolved in alkali. It was then submitted to the usual process of fractional acidification and crystallisation from acetic acid. Pure *trans-syn-trans*- and impure *cis-syn-trans*-acids were isolated.

(ii) *trans-syn-trans*-Acid (300 mg.) was treated similarly for 10 hours. Again, pure *trans-syn-trans*- (m. p. 222—223°) and impure *cis-syn-trans*-acids (m. p. 189—193°) were isolated from the product. The proportion of *cis-trans*-material in these mixtures is of the order of 20%.

cis-anti-cis-*Acid.*—The acid (m. p. 198°) was converted into its anhydride (m. p. 100°; Linstead and Doering, *loc. cit.*). This (89·3 mg. was pyrolysed for 3 hours at 270° under carbon dioxide, and the product separated into anhydride and ketone. The anhydride yielded a mixture of *anti*-acids, m. p. 175—195° (32·6 mg.). The crude semicarbazone of the *anti*-perhydrofluorenone (26·9 mg.) melted at 196—208°. Crystallisation from 96% alcohol yielded 16·2 mg., m. p. 216·5—224° (bath at 215°). A sample of *anti*-semicarbazone prepared from *trans-anti-trans*-perhydrodiphenic acid melted at 220—226° (bath at 215°) and a mixture at the same temperature.

cis-anti-trans-*Acid.*—This rare acid (42 mg.; m. p. 205—206°) was refluxed for 20 minutes at 310° in a stream of nitrogen. The product was worked up in the usual way. The semicarbazone melted at 214—218° after one crystallisation and at 217—220° in admixture with that described above.

The ketonisations of rac.-*trans-anti-trans*- (m. p. 247°) and of *trans-syn-trans*-perhydrodiphenic acid (m. p. 223°) have been described by Linstead and Walpole (*loc. cit.*). Those of the *lævo-cis-syn-trans*- and the *dextro-trans-anti-trans*-acid are recorded in the following paper.

A number of experiments have been made with the object of hydrogenating fluorenone or a hexahydrofluorenone to perhydrofluorenone which could be compared with the products obtained from the perhydrodiphenic acids. These have failed because of the easy elimination of the oxygen under the conditions necessary for perhydrogenation.

We are indebted to Miss Elizabeth J. Cook of Radcliffe College and to Mr. Leonard Spector of Harvard University for assistance in the experimental work.

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293. *The Stereochemistry of Catalytic Hydrogenation. Part IX. Confirmatory Evidence of the Configurations of the Perhydrodiphenic Acids.*

By SELBY B. DAVIS and R. P. LINSTEAD.

Optically active *cis-syn-trans*-perhydrodiphenic acid is racemised when converted into *syn*-perhydrofluorenone, but optically active *trans-anti-trans*-perhydrodiphenic acid gives an active pyroketone. These facts confirm the *syn*- and the *anti*-configurations assigned to the two series of perhydrodiphenic acids by Linstead and Doering.

The hexahydrodiphenic acid of m. p. 221° yields *trans*-hexahydrophthalic acid on ozonisation. This confirms the *cis*- and the *trans*-configurations assigned to the terminal members of the *syn*-series of perhydrodiphenic acids.

The syn- *and* anti-*Configurations of the Backbone.*—In the third paper of this series, Linstead and Doering (*J. Amer. Chem. Soc.*, **1942**, **64**, 2003) proved that, of the six known perhydrodiphenic acids (Linstead and Doering, *ibid.*, p. 1991), those of melting points 280°, 200°, and 223° formed the *syn*- and those of melting points 198°, 206°, and 247° formed the *anti*-series. The present communication presents confirmatory evidence of these configurations by a different method.

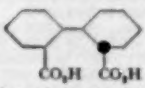
It was shown in the preceding paper (Davis, Doering, Levine, and Linstead) that all six perhydrodiphenic acids yield perhydrofluorenones on pyrolysis. The acids of the *syn*-series give a *syn*-ketone and those of the *anti*-series an *anti*-ketone. As the configuration of the backbone is preserved, there can be no migration of hydrogen from the β-carbon atoms. On the other hand, the α-carbon atoms are so involved because, in each series, essentially the same mixture of ketones is obtained from all three acids.

Optically active perhydrodiphenic acids are now available in both the *syn*- and the *anti*-series (Linstead and Doering, *ibid.*, p. 2003). The molecular dissymmetry of the acids of the *anti*-series involves both the α- and the β-carbon atoms, whereas that of the *cis-syn-trans*-acid (the only active isomeride of the *syn*-series) involves only the α-carbon atoms. It follows that the optical activity of the acids of the *anti*-series should survive pyrolysis to tricyclic ketones,

whereas racemisation should occur during the pyrolysis of the active acid of the *syn*-series. This is illustrated in the diagram.

dextro-cis-syn-trans-Acid — Inactive *syn*-ketone — *dextro-trans-anti-trans*-Acid — *dextro-anti*-Ketone

Formulæ with dots, as shown above, actually represent only one enantiomorphous form of a dissymmetric molecule. The *lævo*-form of the *cis-syn-trans*-acid would be represented in terms of this convention by the formula:



lævo-cis-syn-trans-Acid

We have studied the pyrolysis of the optically active forms of the perhydrodiphenic acids of m. p. 200° (*cis-syn-trans*) and 247° (*trans-anti-trans*) (Linstead and Doering, *loc. cit.*). The ketone obtained from the first acid was optically inactive and yielded an optically inactive mixture of oximes, identical with that obtained from the racemic *cis-syn-trans*-acid (Davis, Doering, Levine, and Linstead, preceding paper). On the other hand the ketone obtained from the active *trans-anti-trans*-acid, after removal of unchanged acid and anhydride, was strongly lævorotatory ($[\alpha]_D$ −130°) and yielded an optically active semicarbazone.

These results conclusively prove that the acid of m. p. 200° belongs to the *syn*-, and that of m. p. 247° to the *anti*-series, in agreement with the configurations assigned by Linstead and Doering (*loc. cit.*). The absence of racemisation of the *anti*-acid shows conclusively that the β-carbon atoms are not involved in pyrolyses of acids of the adipic acid series.

cis- *and* trans-*Configurations in the* syn-*Series.*—Linstead, Davis, and Whetstone (*J. Amer. Chem. Soc.*, **1942**, **64**, 2009) assigned the *cis-cis*-configuration to the *syn*-perhydrodiphenic acid of m. p. 289°. The evidence was in brief: (i) The acid was symmetrical, with similar configurations of the two carboxyl groups. (ii) It was formed by the catalytic hydrogenation of a hexahydrodiphenic acid of m. p. 242°; this hexahydro-acid had a *cis*-configuration because it could be ozonised to *cis*-hexahydrophthalic acid.

In view of the key position of this ozonisation in the general determination of configurations in this group, we thought it advisable to carry out a control series of experiments in the *trans*-series. The geometrical isomeride of the hexahydro-acid of m. p. 242° melts at 221° and gives *cis-syn-trans*-perhydrodiphenic acid on catalytic hydrogenation (Linstead and Davis, *ibid.*, p. 2006). We now find that ozonisation of the latter hexahydro-acid followed by treatment with hydrogen peroxide yields *trans*-hexahydrophthalic acid, identified by comparison with authentic material and by conversion into the known *trans*-dianilide. The ozonisation of the acid, m. p. 221°, thus yields results fully consistent with the previous findings and provides additional evidence for the configurations assigned to the two hexahydrodiphenic acids, m. p.s 242° (*cis*) and 221° (*trans*). These deductions are based on the assumption that, as we think highly probable, there is no inversion of configuration during ozonisation.

During the preparation of (±)-*trans*-hexahydrophthalic acid for comparison with the ozonisation product, it was observed that the melting point of this well-known compound is considerably depressed by the presence of small amounts of impurities, and that the values recorded in the literature are too low. For the inactive *trans*-acid, von Baeyer (*Annalen*, 1890, **258**, 145) gave m. p. 215—221°, Hückel and Goth (*Ber.*, 1925, **58**, 447) 215—216°, and Vavon and Peignier (*Bull. Soc. chim.*, 1929, **45**, 293) 213—218°. An acid melting in this range is, indeed, easily obtained, but on further crystallisation from water it attains a constant melting point of 227—229° (corr.). The melting point is affected to some extent by the rate of heating, but this is less true of the pure acid.

Experimental.

(All m. p.s are corrected. Analyses are by Miss Eleanor Werble.)

Ketonisation of lævo-cis-syn-trans-*Perhydrodiphenic Acid.*—The acid used had been prepared by Dr. W. E. Doering (*J. Amer. Chem. Soc.*, 1942, **64**, 2003). It had m. p. 171—174°, $[\alpha]_D^{20}$ −75° (*c*, 1; in alcohol containing 5% of water). 250 Mg. were heated for 1 hour at 310° in nitrogen. The product was

removed from the reaction vessel with ether and the ether extracted with 5% aqueous sodium hydroxide to remove unchanged acid. The free acid obtained by acidification amounted to only 10 mg. of a sticky gum. The ethereal extract on evaporation gave 120 mg. of a pale yellow oil. Without removal of any anhydride present the oil was dissolved in 6 c.c. of alcohol. The solution gave no observable rotation in a 2-dm. tube. The main portion of the alcohol was removed and the ketone converted into the oxime in the manner described in the preceding paper. The oxime was optically inactive. After 2 crystallisations from methanol it formed fine needles, m. p. 159—165°, $[\alpha]_D^{20}$ 0° ± 1° (*c*, 1; in alcohol containing 5% of water), and was indistinguishable from the mixture of oximes prepared from the racemic *cis-syn-trans*-acid and similarly purified.

Ketonisation of dextro-trans-anti-trans-*Perhydrodiphenic Acid.*—The *dextro*-acid was prepared by resolution with ephedrine, following Slinger (Linstead and Doering, *loc. cit.*). It had m. p. 259—260°, $[\alpha]_D^{20}$ 78° ± 1° (*c*, 1; in 95% alcohol). 175 Mg. of it were heated in a slow stream of nitrogen for 45 minutes at 300—320°. The oily product was extracted with ether and the residue after removal of the ether was warmed for 15 minutes with 3 c.c. of 20% methyl-alcoholic potassium hydroxide. This served to hydrolyse any anhydride present. The solution was evaporated to dryness, and the residue suspended in a little water and extracted thrice with ether. The ethereal extract was dried ($MgSO_4$) and the solvent removed. The residual *lævo-anti*-perhydrofluorenone (83 mg.), $[\alpha]_D^{20}$ −130° ± 0·5° (*c*, 2; in 95% alcohol), was a pale yellow oil with the characteristic pleasant smell of ketones of the group.

The active *anti*-perhydrofluorenone (about 60 mg.) in 1 c.c. of 50% aqueous alcohol was heated on the steam-bath for 40 minutes with sodium acetate (150 mg.) and semicarbazide hydrochloride (100 mg.). The product was cooled in ice, but only a trace of semicarbazone separated. Further quantities of the reagents (half as much as before) were added and the reaction mixture was heated for a further 7 hours. Cooling in ice then precipitated 42 mg. of the semicarbazone of the *lævo*-ketone. Recrystallisation from a large volume of methanol gave the pure *semicarbazone*, irregular laminated plates, m. p. 200—202°, $[\alpha]_D^{20}$ −20° ± 4° (*c*, 0·25; in 95% alcohol). The substance is sparingly soluble in cold 95% alcohol; a 0·5% solution could not be prepared at room temperature (Found: C, 67·8, 67·45; H, 9·0, 8·9. $C_{14}H_{21}ON_3$ requires C, 67·4; H, 9·3%). The *lævo*-semicarbazone in general resembles the corresponding racemate obtained by Vocke (*Annalen*, 1934, **508**, 1) and by Linstead and Walpole (*J.*, 1939, 880), which melts at 216—217°.

Ozonisation of trans-*Hexahydrodiphenic Acid.*—A stream of ozonised oxygen was led for 4 hours through a solution of the acid (*J. Amer. Chem. Soc.*, 1942, **64**, 2006) (1·00 g.; m. p. 220°) in 20 c.c. of warm glacial acetic acid. The product was left overnight with 50 c.c. of 3% hydrogen peroxide and then evaporated to dryness on the steam-bath in a current of air. The dry residue was taken up in 15 c.c. of 10% aqueous sodium carbonate, and the solution extracted with ether and submitted to fractional acidification by Linstead and Doering's method (*loc. cit.*). The first material to separate was unchanged *trans*-hexahydrodiphenic acid (274 mg.). Subsequent addition of a total of 6 c.c. of concentrated hydrochloric acid caused deposition only of a little tar. The aqueous solution was accordingly extracted with ether. This yielded 340 mg. of a mixture of acids which on crystallisation from aqueous acetic acid gave *trans*-hexahydrophthalic acid (71 mg.; 14% calc. on the hexahydrodiphenic acid consumed). The hexahydrophthalic acid so obtained was not quite pure: it melted at 210—214° alone and at 211—215° in admixture with authentic acid. For further identification it was converted into the dianilide. The acid (25 mg.) was dissolved in 2 c.c. of dry ether containing 63 mg. of phosphorus pentachloride. After 20 minutes the solvent was removed and the vessel evacuated. The residue was treated with aniline (60 mg.) in ether. The solvent was removed and the dianilide crystallised twice from glacial acetic acid, forming glistening needles (16 mg.) (Found: C, 74·4; H, 6·5. Calc. for $C_{20}H_{22}O_2N_2$: C, 74·5; H, 6·9%), m. p. 317—318° alone or admixed with authentic *trans*-dianilide. These m. p.s were obtained by the use of a block preheated to 260°. When the capillary was heated slowly from room temperature, the m. p. was 303—304°, in agreement with Stoermer and Steinbeck (*Ber.*, 1932, **65**, 413).

(±)-trans-*Hexahydrophthalic Acid.*—The acid was prepared by the inversion and hydrolysis of methyl *cis*-hexahydrophthalate (cf. Höckel and Goth, *loc. cit.*). The ester was boiled for 5 hours with an excess of 20% methyl-alcoholic potassium hydroxide, and the acid isolated by acidification after the removal of methanol in the usual way. The overall yield of crude *trans*-acid, m. p. 195—214°, was 1·90 g. from 2·25 g. of *cis*-acid. Four successive crystallisations from the minimum amount of water gave the following products: 1·51 g., m. p. 200—217°; 1·23 g., m. p. 215—222°; 0·86 g., m. p. 227—229°; m. p. 227—229°. These m. p.s were obtained by the use of a bath preheated to 260°. Pure *trans*-hexahydrophthalic acid (m. p. 227—229°) forms bold, thick transparent prisms (Found: C, 56·0; H, 7·25. Calc. for $C_8H_{12}O_4$: C, 55·8; H, 7·0%). The anhydride, made from the pure acid and acetyl chloride, melts at 142·5—144° (lit., 140°) and the dianilide at 317—318° (see above). The dianilide is practically unaffected by being refluxed (18 hours) with 80% acetic acid, in agreement with Stoermer and Steinbeck (*loc. cit.*).

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294. *The Stereochemistry of Catalytic Hydrogenation. Part X. The Hydrogenation of* trans-as-*Octahydrophenanthrene Derivatives. A New Form of the Perhydrophenanthrene Ring and a Model for the Inversion of the 6-Keto-steroids.*

By R. P. Linstead and Richard R. Whetstone.

The hydrogenation, over platinum, of *trans-as*-9-keto-octahydrophenanthrene and of the two alcohols derived from it has been studied. There is formed a mixture of 60% of *cis-syn-trans*- and 40% of *cis-anti-trans*-perhydro-9-phenanthrol. The *cis-syn-trans*-alcohol on oxidation with chromic acid yields the corresponding *cis-syn-trans*-ketone, and on dehydration followed by ozonisation gives *cis-syn-trans*-perhydrodiphenic acid. As the corresponding *trans-syn-cis*-compounds are known, the new substances must belong to the *cis-syn-trans*-series.

The *cis-anti-trans*-alcohol on chromic acid oxidation gives the corresponding *cis-anti-trans*-ketone, readily inverted to the known *trans-anti-trans*-ketone, thus proving the structure and configuration.

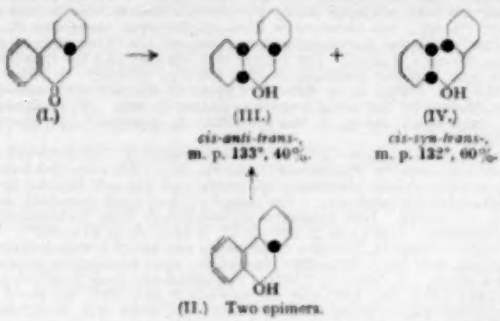
It is shown that the results conform to the principles of one-sided addition and of catalyst hindrance already enunciated.

Derivatives of four out of six of the possible forms of the perhydrophenanthrene ring are therefore now known. Five of the possible eight C_{14} ketones and nine of the possible sixteen C_{14} alcohols have been isolated.

In a previous paper (Linstead, Whetstone, and Levine, *J. Amer. Chem. Soc.*, 1942, **64**, 2014) it was shown that classical stereochemistry allowed for the existence of six perhydrophenanthrenes, eight inactive ketones with a carbonyl group on C_{14}, and sixteen inactive alcohols derived from them. Three of the possible ketones and four of the alcohols were described and the configurations of these ketones and of all but one of the alcohols were proved.

In the present paper the further investigation of this group is described and the isolation of two more stereoisomeric ketones and of five more alcohols is reported, together with the proof of their configurations.

Our earlier work had involved the hydrogenation of 9-phenanthrol, of *cis*-9-keto-*as*-octahydrophenanthrene, and of derived alcohols. We have now taken up the study of the corresponding octahydro-compounds of the *trans*-series. The parent ketone (I) (Cook *et al.*, *J.*,

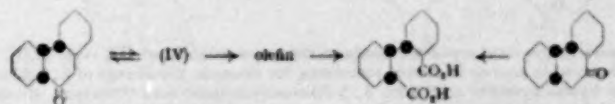


1936, 71; 1939, 168; Linstead, Whetstone, and Levine, *loc. cit.*) undoubtedly contains a *trans*-locking of the rings, the *cis*-configuration of its stereoisomeride having been proved conclusively in our earlier work. It will be noted, moreover, that the further hydrogenation of the *trans*-octahydro-ketone invariably produces material for which one *trans*-junction can be independently established. The substances hydrogenated were the *trans*-octahydro-ketone, m. p. 96°, and the two derived epimeric secondary alcohols (II), m. p.s 91° and 101°, described in our previous paper. Hydrogenations, which were carried out with Adams's platinum oxide, were more difficult than in the *cis*-series. No reaction occurred in alcohol alone but in the presence of a little acetic acid reduction was smooth and there was little formation of hydrocarbon. The same product was obtained from all three starting materials. It was a mixture of two *per-*

hydro-9-phenanthrols, which have been proved to have the *cis-anti-trans*- (III) and *cis-syn-trans*-configurations (IV).*

The two alcohols had practically the same melting point but a mixture melted some 25° lower. Their separation was not easy (see Experimental section) but prior oxidation to the corresponding ketones was helpful as a convenient separation of the two series through the oximes was possible.

Oxidation of the *cis-syn-trans*-alcohol † (IV) gave cis-syn-trans-9-*ketoperhydrophenanthrene* (V), m. p. 72° (*oxime*, m. p. 206°). Reduction of this ketone with sodium in moist ether re-formed the *cis-syn-trans*-alcohol, m. p. 132°, whereas catalytic hydrogenation slowly yielded an *epimer*, m. p. 77°. The determination of configuration of these materials was difficult. No perhydrodiphenic acid could be isolated by nitric acid oxidation and attempts to convert the ketone into a 9 : 10-quinone by means of selenium dioxide or *iso*amyl nitrite were abortive. However the perhydro-alcohol, m. p. 132°, was dehydrated to an olefin which on ozonisation yielded the *cis-syn-trans*-perhydrodiphenic acid (VI) of Linstead and Doering (*J. Amer. Chem. Soc.*, 1942, **64**, 1991). This means that the new ketone and alcohol must belong to either the *cis-syn-trans*- (V) or the *trans-syn-cis*-series (VII). (The first prefix is by convention assigned to



(V.), m. p. 72° (VI.) (VII.), m. p. 57°

the configuration of the ring locking *adjacent* to the functional group.) But Linstead, Whetstone, and Levine (*loc. cit.*) have already isolated the *trans-syn-cis*-ketone (VII). Its structure is certain because (*a*) it yields the acid (VI) on oxidation and (*b*) it is formed by the inversion at the bridgehead next to C_{10} of a ketone known to have the *cis-syn-cis*-configuration. Hence the new compounds belong to the *cis-syn-trans*-series (V).

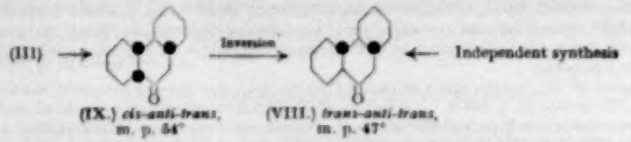
It is an interesting fact that the new ketone (V) is not inverted in configuration under the conditions which customarily convert *cyclo*hexane ketones with a carbonyl group next to a *cis*-bridgehead into their *trans*-isomerides, for example *cis*- into *trans*-α-decalone and *cis-syn-cis*-9-ketoperhydrophenanthrene into the *trans-syn-cis*-isomeride (VII). However, it would appear from Stuart models that the *trans-syn-trans*-ring system [which would be formed by the inversion of (V)] may be less stable than the *cis-syn-trans*-system. This illustrates the danger of argument by analogy in this field, and the need for the determination of configuration by unequivocal methods.

The second substance formed in the catalytic hydrogenation of *trans*-9-keto-*as*-octahydrophenanthrene and its derived alcohols was a *perhydro-9-phenanthrol* of m. p. 133°. Oxidation of this substance with chromic acid yielded a new 9-*ketoperhydrophenanthrene* of m. p. 54°, hydrogenation of which re-formed the parent alcohol. The ketone yielded an unstable *oxime*, m. p. 140°, which on acid hydrolysis yielded an isomeric, stable ketone, m. p. 47° (oxime, m. p. 233°). Isomerisation of the ketone of m. p. 54° into that of m. p. 47° could also be effected with alcoholic alkali. The inverted ketone, m. p. 47°, was identified by mixed melting point determinations of both ketone and oxime with the 9-keto-perhydrophenanthrene (" Form 3 ") made by Linstead and Walpole (*loc. cit.*) from Rapson and Robinson's unsaturated ketone (*J.*, 1935, 1285). This substance undoubtedly has the *trans-anti-trans*-configuration (VIII) : it can be oxidised to *trans-anti-trans*-perhydrodiphenic acid (Linstead and Walpole, *J.*, 1939, 850; Linstead and Doering, *J. Amer. Chem. Soc.*, 1942, **64**, 2003; Linstead, Davis, and Whetstone, *ibid.*, p. 2009). It follows with certainty that the new ketone, m. p. 54°, has the *cis-anti-trans*-configuration (IX) and so does the parent alcohol (III). They are the first derivatives of this form of the perhydrophenanthrene ring to have been made. Derivatives of four (*cis-syn-cis*, *cis-syn-trans*, *cis-anti-trans*, *trans-anti-trans*) of the six basic types are now known.

Catalytic hydrogenation of the ketone, m. p. 47°, gave a new trans-anti-trans-*perhydro-9-phenanthrol*, m. p. 80°, whereas alkaline reduction gave the epimer, m. p. 119°, already reported by Linstead and Walpole (*loc. cit.*).

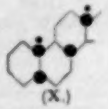
* For nomenclature see Linstead, *Chem. and Ind.*, 1937, **56**, 510; Linstead and Walpole, *J.*, 1939, 842.
† The correct configurations are anticipated at this point for the sake of clarity.

The preparation and inversion of the *cis-anti-trans*-ketone (IX) is noteworthy for three reasons. First, the inversion of *cis-trans*- to *trans-trans*-form occurs in the *anti*- but not in the



(IX.) *cis-anti-trans*, m. p. 54° (VIII.) *trans-anti-trans*, m. p. 47°

syn-series. Secondly, the *cis-anti-trans*-arrangement of the perhydrophenanthrene ring is that which is present in the normal series of steroids, *i.e.*, that including 5-*iso*androstane, pregnane, cholanic acid, coprostane, and their derivatives (X). Thirdly, the inversion of the



(X.)

* These dots represent methyl groups above the rings.

cis-anti-trans- to the *trans-anti-trans*-configuration, now established (IX ⟶ VIII), is parallel to those observed in analogous steroid structures, for example, the change of 3 : 6-diketocholanic acid (from hyodeoxycholic acid) into 3 : 6-diketo*allo*cholanic acid (Windaus, *Annalen*, 1926, **447**, 253). The inversion of *cis-anti-trans*- to *trans-anti-trans*-9-ketoperhydrophenanthrene provides a much safer model for the changes of 6-keto-steroids than does that (*cis*- to *trans*-α-decalone) previously used.

It has also been possible to study one other aspect of the *syn*-perhydrophenanthrol series. In our previous work we had identified with certainty one *cis-syn-cis*-alcohol, m. p. 111°, and one *trans-syn-cis*-alcohol, m. p. 89°. There was in addition an alcohol of m. p. 67°, prepared by Marvel and White (*J. Amer. Chem. Soc.*, 1940, **62**, 2739) by the reduction of 9-phenanthrol over nickel. Oxidation of this alcohol with hot chromic acid had given a 9-ketoperhydrophenanthrene, m. p. 57°, doubtless identical with the *trans-syn-cis*-ketone of the same melting point which we had prepared by another method. This means that the alcohol of m. p. 67° is an epimer of either the known *cis-syn-cis*- or the *trans-syn-cis*-alcohol. If it is a *cis-syn-cis*-compound the oxidation to the ketone must have been accompanied by inversion. This is quite feasible; we have observed the same thing in the oxidation of the *cis-syn-cis*-alcohol, m. p. 111°, with hot chromic acid.

We have now reduced our *trans-syn-cis*-9-ketoperhydrophenanthrene with sodium in alcohol to a new 9-*perhydrophenanthrol*, m. p. 100°. This must be the missing epimer of the *trans-syn-cis*-series. Hence we can provisionally say that Marvel and White's alcohol (m. p. 67°) is the missing epimer of the *cis-syn-cis*-series; its direct oxidation to a perhydrodiphenic acid is desirable.

The present state of knowledge of the 9-substituted perhydrophenanthrenes is summarised in the table, which gives the melting points of the known compounds.

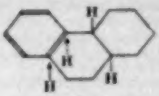
syn-Series:	Ketones.	Alcohols.	*anti*-Series:	Ketones.	Alcohols.
cis-cis	44° [1]	111° [1], 67° [4]	*cis-cis*	—	— —
trans-cis	57° [1,4]	100° [2], 89° [1]	*trans-cis*	—	— —
cis-trans	72° [3]	132° [3], 77° [3]	*cis-trans*	54° [3]	133° [3] —
trans-trans	—	— —	*trans-trans*	49° [2,3]	119° [2,3] 80° [3]

[1] Linstead, Whetstone, and Levine, *loc. cit.* [2] Present paper. [3] Linstead and Walpole, *loc. cit.* [4] Marvel and White, *loc. cit.*

With the exception of the *trans-syn-cis*-compounds, which are intermediate in type, the perhydro-alcohols fall into two classes. Four alcohols are high-melting (111° to 133°), moderately soluble and crystallise well. The other three resemble the related ketones in their physical properties, being lower-melting, more soluble, and much harder to crystallise. Each epimeric pair has one member of each type. The higher-melting epimer was always isolated readily from the hydrogenation of octahydrophenanthrene compounds. This is probably deceptive; the low-melting epimers were fairly certainly present in the mother-liquors, which by oxidation usually yielded some 10—30% of perhydro-ketones. Reduction of the perhydro-ketones to alcohols gave less uniform results. Two ketones (*cis-syn-trans*, *trans-anti-trans*)

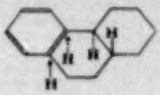
yielded the lower-melting alcohol by catalytic hydrogenation and the epimers by reduction with sodium. Two other ketones (*cis-syn-cis*, *cis-anti-trans*) were catalytically hydrogenated to the higher-melting alcohols and a low-melting isomeride could not be isolated. The distinction in physical properties of the two series must correspond with the packing of the molecules in the crystal lattice, which is affected by the relation in space of the hydroxyl group to the rest of the structure.

We must now review the new results in their bearing on the stereochemistry of hydrogenation of aromatic rings. The first point is that over Adams's platinum at room temperature the aromatic ring of *trans-as*-octahydrophenanthrene is hydrogenated to give *cis*-compounds, in accordance with the principle of one-sided addition (Linstead, Doering, Davis, Levine, and Whetstone, *J. Amer. Chem. Soc.*, 1942, **64**, 1985). The second point is that hydrogenations go both *syn*- (60%) and *anti*- (40%) in the *trans*-series, whereas the corresponding *cis*-compounds are hydrogenated only to *syn*-products. At first sight this appears anomalous but consideration shows that it is to be expected on the hypothesis of catalyst hindrance (Linstead *et al.*, *loc. cit.*, p. 1989). According to this, hindrance between the catalyst and substrate will effect adsorption



(XIa.)

Sorption leading to *anti*-configuration.



(XIb.)

Sorption leading to *syn*-configuration.

selectively so that one particular spatial arrangement may be expected to be favoured and the alternative inhibited. Hydrogenation will follow correspondingly, the hydrogen entering the molecule to give the configuration consequential on the preferred adsorption. This readily explains why *cis-as*-octahydrophenanthrene derivatives give *cis-syn-cis*-perhydro-compounds.

The case of *trans-as*-octahydrophenanthrene is different. The *trans*-decalin part of the molecule is approximately planar and the hindrance anticipated between the catalyst and one arrangement of the substrate (XI*a*) should not differ greatly from that with the alternate arrangement (XI*b*). There is no *prima facie* reason why adsorption should not occur in both ways. Hence we should expect both *cis-anti-trans*- and *cis-syn-trans*-materials to be produced, which is precisely what occurs. It would be premature to regard the hypothesis of catalyst hindrance as proved but it is interesting to find results such as these in line with its requirements. It may also be significant that in the *trans*-series, where both positions of sorption are somewhat hindered, hydrogenation is less ready than in the *cis*-series where one position of sorption is free from hindrance.

In addition to the above results, we have made some progress towards obtaining the various parent hydrocarbons, the perhydrophenanthrenes, in stereochemically homogeneous forms of known configuration. This is being further investigated and it is hoped to describe it later.

Experimental.

Hydrogenation of trans-9-*Keto-as-octahydrophenanthrene* (I).—A solution of the ketone, m. p. 95—96° (6·2 g.), prepared by the method of Linstead, Whetstone, and Levine (*loc. cit.*) in absolute alcohol (75 c.c.) containing 3 drops of acetic acid over Adams's platinum oxide (0·6 g.) took up 3·6 moles of hydrogen at atmospheric pressure in 4 days. After removal of the catalyst and solvent, the residual oil was diluted with hexane (30 c.c.) and set aside. There was deposited a solid (A.) (2·3 g.), m. p. 105—115°, which was dissolved in hexane (20 c.c.) and benzene (8 c.c.). The solution on being allowed to cool slowly deposited fine needles (B) (0·95 g.), m. p. 126—130°. Crystallisation of this from ether gave long prisms of cis-syn-trans-*perhydro-9-phenanthrol* (IV), m. p. 131·5—132° (Found: C, 80·8; H, 11·4. $C_{14}H_{24}O$ requires C, 80·7; H, 11·6%). The filtrate from (*B*), when kept overnight, deposited a solid (C) (0·25 g.), m. p. 129—132°, which on crystallisation from hexane yielded rosettes of fine, silky fibres of cis-anti-trans-*perhydro-9-phenanthrol* (III), m. p. 133—133·5° (Found: C, 81·0; H, 11·7%). A mixture of the two alcohols melted at 105—115°. Evaporation of the filtrate from (*C*) gave a mixture (*D*) of the two alcohols in approximately equal amounts. The m. p. of this was raised by admixture with either of the components. Some separation could be effected by slow evaporation of ethereal solutions, but the best technique for both this mixture and the mother-liquor from the original solid hydrogenation product (*A*) was through oxidation to the ketones (see below).

The two pure *trans-as*-octahydro-9-phenanthrols (m. p.s 90° and 100°; Linstead, Whetstone, and Levine, *loc. cit.*) were similarly hydrogenated. Each gave the same two perhydro-phenanthrols in about the same proportions.

cis-syn-trans-9-*Ketoperhydrophenanthrene* (V).—The *cis-syn-trans*-alcohol, m. p. 129—132° (0·50 g.), was oxidised with chromic oxide in acetic acid, and the ketone (0·42 g.; m. p. 69—71°) isolated in the

usual way. Two crystallisations from light petroleum yielded long needles of pure *cis-syn-trans-9-ketoperhydrophenanthrone*, m. p. 71·5—72° (Found: C, 80·7; H, 10·9. $C_{14}H_{22}O$ requires C, 81·5; H, 10·6%). The *oxime*, which was formed readily in the cold, crystallised from alcohol in fine needles, m. p. 205—206° (Found: C, 76·2; H, 10·4. $C_{14}H_{23}ON$ requires C, 76·0; H, 10·5%). Hydrolysis of the oxime with boiling 5% sulphuric acid regenerated the parent ketone. The ketone was not inverted by heating (i) in hot alcoholic sodium ethoxide for 90 minutes, (ii) with hydrochloric acid in boiling ether for 9 hours, or (iii) alone at 200° for 3 hours.

Reduction of the ketone (0·20 g.) with sodium (0·25 g.) in moist ether (20 c.c.) gave 0·17 g. of the *cis-syn-trans*-alcohol (0·17 g.), m. p. 132°, already reported. The ketone (320 mg.) was hydrogenated over Adams's catalyst in alcohol (20 c.c.) containing acetic acid (2 c.c.). (In pure alcohol the hydrogenation was very slow.) The epimeric *cis-syn-trans-perhydro-9-phenanthrol* formed (290 mg.; m.p. 73—75°) was very soluble in organic solvents. Two recrystallisations raised the m. p. to 76—77° (Found: C, 80·96; H, 11·75. $C_{14}H_{26}O$ requires C, 80·7; H, 11·6%).

No solid acid could be isolated after oxidation, by nitric acid, of the *cis-syn-trans*-ketone or either of the derived alcohols. The technique used by Linstead and Doering (*loc. cit.*) for the isolation and purification of perhydrodiphenic acids was applied to the products without success. Reaction of the ketone with isoamyl nitrite (Litvan and Robinson, *J.*, 1938, 1977) or with selenium dioxide in dioxan or in acetic anhydride (cf. Evans, Ridgion, and Simonsen, *J.*, 1934, 137) failed to yield any 9 : 10-quinone.

The *cis-syn-trans*-perhydrophenanthrol, m. p. 132° (450 mg.), was dehydrated with potassium hydrogen sulphate (900 mg.) at 200° for 3 hours. The resulting liquid olefin was ozonised and the ozonide decomposed by evaporation with 3% hydrogen peroxide. The acid product in aqueous sodium carbonate was fractionally acidified. The third treatment yielded a crystalline solid (25 mg.; m. p. 190—195°) which after crystallisation from acetic acid melted at 196—198° alone or in admixture with authentic *cis-syn-trans*-perhydrodiphenic acid (Linstead and Doering, *loc. cit.*).

cis-anti-trans- *and* trans-anti-trans-*Series*. *cis-anti-trans*-Perhydro-9-phenanthrol (III), m. p. 135° (200 mg.), was oxidised in the cold with chromic and acetic acids. The ketone, isolated in the usual way, melted at 52—54° (110 mg.).

cis-anti-trans-9-*Ketoperhydrophenanthrone* forms needles (from light petroleum), m. p. 53—54° (Found: C, 81·2; H, 10·75. $C_{14}H_{22}O$ requires C, 81·5; H, 10·75%). The oxime was formed rapidly at room temperature. Crystallisation from alcohol, in which it was freely soluble, lowered its initial m. p. of 145—148° to 140—143°, presumably because inversion had commenced. Hydrolysis of the oxime with boiling 5% sulphuric acid yielded the *trans-anti-trans*-ketone (see below).

Catalytic hydrogenation of the *cis-anti-trans*-ketone (100 mg.) in alcohol containing a few drops of acetic acid (Adams's catalyst) yielded 80 mg. of the *cis-anti-trans*-alcohol, m. p. 132—133°, already reported.

The *cis-anti-trans*-ketone (80 mg.) was boiled for 105 minutes with sodium ethoxide (from 0·3 g. of sodium and 5 c.c. of alcohol). The product was poured into water and isolated by means of ether. After crystallisation of the residue from light petroleum, 10 mg. of *trans-anti-trans*-ketone were obtained, having m. p. and mixed m. p. 44—46°. The oxime had m. p. and mixed m. p. 230—233°.

The *trans-anti-trans*-ketone (240 mg.) (Linstead and Walpole, *loc. cit.*) rapidly took up one mole of hydrogen over Adams's catalyst, in alcoholic solution. Crystallisation of the product from light petroleum gave 120 mg. of a new trans-anti-trans-*perhydro-9-phenanthrol* (m. p., crude, 76—78°). Two recrystallisations from light petroleum, followed by sublimation at 90°/5 mm., gave the analytical sample, m. p. 80—80·5° (Found: C, 81·0; H, 11·8. $C_{14}H_{26}O$ requires C, 80·7; H, 11·6%). The epimeric alcohol was prepared in good yield by the reduction of the ketone with sodium in moist ether. It had m. p. 116—118°, in agreement with Linstead and Walpole.

Separation of cis-syn-trans- *and* cis-anti-trans-*Material*.—It has been said that the solid product (*A*; p. 1431) from the hydrogenation of *trans*-9-keto-*as*-octahydrophanthrene was separated by crystallisation into the *cis-syn-trans*- and *cis-anti-trans*-alcohols and a mixture (*D*; p. 1431). This mixture (900 mg.) was oxidised with chromic oxide in the usual way. Crystallisation of the product from light petroleum gave 210 mg. of *cis-syn-trans*-ketone (m. p. 67—68°). The residue from this, which could not be further crystallised, was converted into oximes (490 mg.), separated by fractional crystallisation from alcohol into *cis-syn-trans*- (120 mg.; m. p. 195—198°) and *cis-anti-trans*-oxime (350 mg.; m. p. 135—145°). (*D*) thus contains alcohols of the two series in about equal amounts.

The mother-liquor from the original solid hydrogenation product (*A*) was also examined. Some 9 g. of this were accumulated. Vacuum-distillation yielded 4·0 g. of non-viscous liquid, boiling below 125°/5 mm. and mainly composed of hydrocarbons, together with 5·1 g. of a viscous oil, b. p. 125—140°/5 mm. Oxidation of the high-boiling fraction with chromic acid yielded a mixture of ketones which was converted into oximes at room temperature. The following crops were removed separately: (i) after 5 minutes, m. p. 190—220°, 1·8 g., (ii) after another 30 minutes, m. p. 192—193°, 1·3 g., (iii) after storage overnight, m. p. 180—185°, 0·3 g. Crop (i) was separated into *trans-anti-trans*-, m. p. 230—232° (1·6 g.), and *cis-syn-trans*-oxime, m. p. 195—200° (0·2 g.). Crops (ii) and (iii) yielded 1·0 g. of *cis-syn-trans*-oxime, m. p. 200—202°. The *trans-anti-trans*-material was presumably formed by inversion at the stages of oxidation and oximation, but we cannot exclude the possibility that some was present in the original hydrogenation product.

From a review of the constituents of the various products, it is concluded that the hydrogenation of the *trans*-octahydro-ketone yielded about 60% of perhydrophenanthrols, of which 60% had the *cis-syn-trans*- and 40% the *cis-anti-trans*-configurations.

We are indebted to Miss Eleanor Werble and Mr. W. G. Dauben for the microanalyses.

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295. *Deoxy-sugars. Part XII. Experiments with the O- and N-Glycosides of Some Deoxy-sugars.*

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The preparation is described of some *O*- and *N*-glycosidic derivatives of 2-deoxy-pentoses and -hexoses and of the *O*-glycosides of 2 : 3-dideoxy-D-glucose. Comparative measurements are reported on the rates of acid hydrolysis of these glycosides, showing that the methylene groups in these sugars exert a profound effect on substituents attached at $C_{(1)}$ and increase their lability.

In earlier communications in this series (*J.*, 1949, 2841, 2846) it has been shown that a deoxy-group at $C_{(2)}$ in pentoses and hexoses exerts a profound effect on the glycosidic centre in these sugars. Methylglycosides of 2-deoxy-sugars are hydrolysed by acid much more rapidly than are the corresponding derivatives of the normal analogous sugar. In nucleic acids the basic constituents are linked to the sugar residues by *N*-glycosidic attachments, so we considered it worth while to study the effect of a deoxy-group at $C_{(2)}$ on *N*-glycosides of pentoses and hexoses. Sugar anilides were chosen as convenient derivatives for this purpose. For most sugars, the aniline derivatives are highly crystalline and consequently have been found useful for the characterisation of sugars. Until recently there was very little clear evidence concerning the structure of sugar anilides in general. It had not been demonstrated conclusively for example whether they were all *N*-glycosides or whether some were Schiff's bases. Even on the assumption that they were of the former structure, the nature of the lactol ring was unknown. It should be noted that Irvine and McNicoll (*J.*, 1910, 1449), from methylation studies, had obtained some indications that galactose anilide was a *N*-glycoside having a 1 : 5-lactol ring.

Recent work by Butler, Smith, and Stacey (*J.*, 1949, 3371) with galactose anilide and its acetylation products led to the isolation of two forms of the acetylated anilide which were considered to be α- and β-anomers of pyranose type, thereby providing further evidence in support of the ring structure for anilides. Furthermore, some of us, with other colleagues (Butler, Overend, Smith, and Stacey, *Chem. and Ind.*, 1949, 551) have proved conclusively that anilides in their normal crystalline form are *N*-glycosides and not Schiff's bases. We have now extended this work into the deoxy-sugar series.

Crystalline ***anilides*** of 2-deoxy-D-galactose, 2-deoxy-D-glucose, 2-deoxy-L-ribose, and 2-deoxy-D-xylose have been obtained by the usual method for the synthesis of anilides, namely by heating a solution or suspension of the sugar with freshly distilled aniline in absolute or aqueous ethanol (cf. Kent, Stacey, and Wiggins, *J.*, 1949, 1232; Overend, Staněk, and Stacey, *ibid.*, p. 2841). These derivatives are excellent for the characterisation of the sugars named (see also Overend and Stacey, *ibid.*, p. 1358). The products exhibited mutarotation in solution in pyridine or dry methanol, indicating that in all probability they were *N*-glycosides. Attempts to get further evidence to support these optical rotational data by chemical methods were unsuccessful. Triacetyl D-galactal which is known to have a pyranose structure (Levene and Tipson, *J. Biol. Chem.*, 1931, **93**, 631) was treated with bromine and yielded 3 : 4 : 6-triacetyl 1 : 2-dibromo-1 : 2-dideoxy-D-hexose (cf. Fischer, *Ber.*, 1920, **53**, *B*, 509), which, however, on reaction with aniline in the presence of excess of silver carbonate underwent extensive decomposition. Similarly application of Butler, Smith, and Stacey's methods (*loc. cit.*), which proved successful with galactose anilide, were found to be too vigorous for the more unstable 2-deoxy-sugars. Either acetylation or methanesulphonation of the anilides of 2-deoxy-D-galactose, 2-deoxy-D-glucose, and 2-deoxy-L-ribose resulted in the isolation of syrupy mixtures from which suitable acetylated or methanesulphonated α- and β-anomers of the anilides could not be isolated. With 2-deoxy-D-glucose anilide it did seem that some of the required products were present in the syrupy acetylation mixture, since deacetylation by sodium methoxide resulted in the formation of some of the starting material. Lee *et al.* (*J. Org. Chem.*, 1946, **11**, 75) showed that, when an acidified aqueous solution of ribose (pH 3—5) is treated with aniline in the cold, an anilide is formed which differs from that obtained by the customary procedure. They proposed that their new anilide possessed a pyranose structure, and that the product obtained by the normal route was of the furanose form. From their results it would appear that the furanose form of ribose anilide is more stable than the pyranose form. Application of their method to 2-deoxy-sugars yielded the same anilides as those already described. The effect observed by Lee *et al.* (*loc. cit.*) does not appear to be general since Butler, Smith, and Stacey (*loc. cit.*) found that galactose would yield only one anilide. Since anilides in the 2-deoxy-sugar series are so labile we considered that some physical measurements might

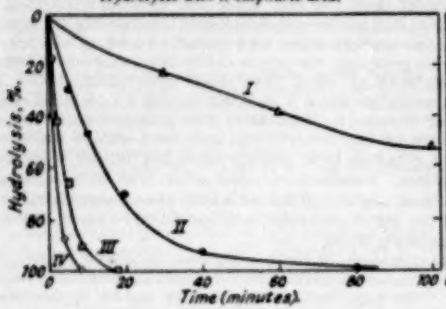
be a useful approach. In collaboration with Dr. H. P. Koch of the British Rubber Producers Research Association, Welwyn Garden City, it was demonstrated conclusively by infra-red absorption spectra measurements that the C=N linkage was absent in 2-deoxy-sugar anilides. Consequently they could not be of the Schiff's base type, but were *N*-glycosides. Furthermore, by analogy with other glycosides and anilides of known structure, it was clear that they possessed the 1 : 5-lactol (pyranose) ring.

The following compounds were used: (i) n-propylaniline, (ii) benzylideneaniline, (iii) D-arabinose, (iv) α-methyl-D-arabopyranoside, (v) 1 : 2-*iso*propylidene D-glucofuranose, (vi) 2-deoxy-D-ribose anilide, (vii) 2-deoxy-D-glucose anilide. The band positions observed were: (*a*) unconjugated phenyl in (i), (vi), and (vii) at 1600 cm.$^{-1}$; (*b*) conjugated phenyl in (ii) at 1572 cm.$^{-1}$; (*c*) C=N in (ii) at 1625 cm.$^{-1}$ (conjugated); (*d*) CH·OH in (iii), (iv), (v), (vi), and (vii) at 1050—1080 cm.$^{-1}$; (*e*) CH_2·OH (?) in (v) and (vii) only at 1030 cm.$^{-1}$; (*f*) pyranose ring in (iii), (iv), (vi), and (vii) at 985—995(??) cm.$^{-1}$; (*g*) >NH was not identified in (vi), (vii), or (i).

The rates of hydrolysis of these anilides were then measured quantitatively and compared with those already reported for some *O*-glycosides of the same sugars. Preliminary studies with 0·5% formic acid confirmed our observations that 2-deoxy-sugar anilides were highly labile.

FIG. 1.

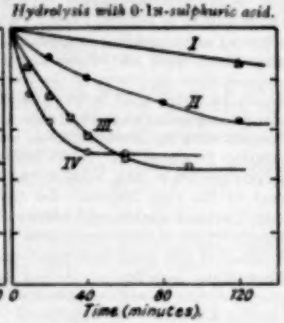
Hydrolysis with N-*sulphuric acid.*



I. D-*Glucose anilide.*
II. D-*Galactose anilide.*
III. 2-*Deoxy*-D-*glucose anilide.*
IV. 2-*Deoxy*-D-*galactose anilide.*

FIG. 2.

Hydrolysis with 0·1N-*sulphuric acid.*



I. D-*Glucose anilide.*
II. D-*Galactose anilide.*
III. 2-*Deoxy*-D-*glucose anilide.*
IV. 2-*Deoxy*-D-*galactose anilide.*

The rates of hydrolysis of anilides in the normal and corresponding 2-deoxy-sugars were compared by a method similar to that described by Hanaoka (*J. Biochem. Japan*, 1940, **95**, 31). The results are shown in Figs. 1—4. Figs. 1 and 2 refer to the hydrolysis of anilides of hexoses and 2-deoxy-hexoses, with N- and 0·1N-sulphuric acid (concentrations quoted refer to the acid before addition to the solution of sugar anilide). Figs. 3 and 4 refer to the corresponding pentose derivatives. The hydrolyses were followed polarimetrically at room temperature, after addition of mineral acid to a solution of the sugar anilide which had mutarotated to equilibrium in dry methanol. Equimolecular solutions of the sugar derivatives were used. Although hydrolysis of the normal sugar anilides by 5N-sulphuric acid could be followed polarimetrically, the rate was much too rapid in the deoxy-sugar series with acid of this concentration. However, the end values were identical with those obtained by using more dilute acid (N-H_2SO_4). With 0·1N-sulphuric acid, the normal sugar anilides were not always completely hydrolysed, since the liberated aniline reduced the acid concentration sufficiently to terminate eventually the hydrolysis reaction. In such cases, aniline sulphate could be isolated. The isolation of this salt, coupled with the fact that the end values obtained for the optical rotations after further additions of acid corresponded to those for solutions of the free sugars at equilibrium, was taken as indicating that the acid treatment resulted mainly in hydrolysis of the anilides. Separate experiments indicated that mutarotational changes resulting from the free sugars formed by the hydrolyses did not interfere with the results, except perhaps in the case of galactose, for which the rate of mutarotation of the free sugar in acid solution was comparable with the rate of hydrolysis of its anilide with N-sulphuric acid. However, since some discoloration was noted during the experiments, it was inferred that some secondary change (re-arrangement)

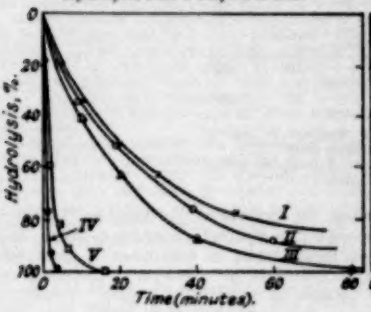
accompanied the main reaction, *e.g.*, possibly some re-arrangement of the type indicated by Gottschalk and Partridge (*Proc. Biochem. Soc.*, in the press).

From the graphs of the rotational changes the degree of hydrolysis was calculated by a process of integration, and these are the results shown in Figs. 1—4. Reference to Figs. 1 and 2 shows that 2-deoxy-sugar anilides in the hexose series are hydrolysed much more rapidly than the corresponding normal sugar anilides. Similar results are obtained in the pentose series (see Figs. 3 and 4).

Comparison with the studies of Overend, Stacey, and Staněk (*J.*, 1949, 2841) revealed that *N*-glycosides (anilides) of 2-deoxy-sugars are more labile than the *O*-glycosides. This property is closely similar to that of corresponding derivatives of normal sugars. Since for both *O*- and *N*-glycosides it is clear that a deoxy-group at $C_{(2)}$ of a sugar exerts an influence on the glycosidic centre, it was decided to investigate further the effect of additional methylenic groups by preparing some dideoxy-sugar derivatives, *e.g.*, particularly the 2 : 3-dideoxy-derivatives. Because of the greater ease of manipulation the *O*-glycosides were used, and for comparative purposes the ethyl glycosides were prepared. α- and β-Ethyl-D-glucopyranosides were made

FIG. 3.

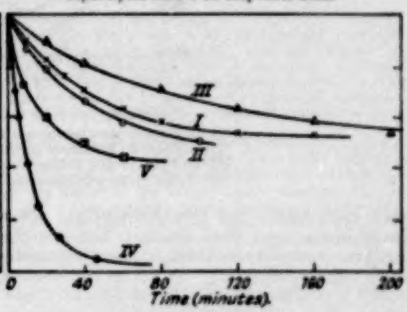
Hydrolysis with N-sulphuric acid.



I. D-*Ribopyranose anilide.*
II. D-*Ribofuranose anilide.*
III. D-*Xylose anilide.*
IV. 2-*Deoxy*-L-*ribose anilide.*
V. 2-*Deoxy*-D-*xylose anilide.*

FIG. 4.

Hydrolysis with 0·1N-sulphuric acid.



I. D-*Ribopyranose anilide.*
II. D-*Ribofuranose anilide.*
III. D-*Xylose anilide.*
IV. 2-*Deoxy*-L-*ribose anilide.*
V. 2-*Deoxy*-D-*xylose anilide.*

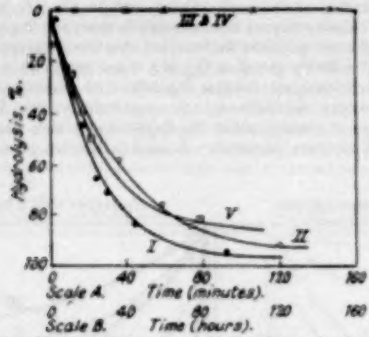
according to the usual methods (see Fischer, *Ber.*, 1895, **28**, 1154; Ferguson, *J. Amer. Chem. Soc.*, 1932, **54**, 4086) and further characterised as their tetra-*p*-nitrobenzoates. α-Ethyl-D-glucofuranoside 5 : 6-carbonate was made by the method of Haworth and Porter (*J.*, 1929, 2796). Treatment of 2-deoxy-D-glucose with 0·2% ethanolic hydrogen chloride resulted in the formation of an *ethyl-2-deoxy-D-glucoside*. The same glycoside was obtained, in very poor yield, from the action of 1·6% ethanolic hydrogen chloride on D-glucal (an unidentified oil was also obtained and this will be the subject of a subsequent communication). Hydrolysis of this glycoside with N-hydrochloric acid resulted in the re-formation of 2-deoxy-D-glucose which was isolated as its dibenzyl mercaptal (cf. Overend, Stacey, and Staněk, *loc. cit.*). Oxidation by lead tetra-acetate resulted in the uptake of 1 mole of oxidant.

In like manner ethyl-2-deoxy-D-glucoside reduced one mole of sodium metaperiodate, but no formaldehyde was formed, indicating that the glycoside has a pyranose structure. Treatment of it with *p*-nitrobenzoyl chloride in pyridine yielded 3 : 4 : 6-*tri*-p-*nitrobenzoyl ethyl-2-deoxy*-D-*glucoside*. A crystalline 3 : 4 : 6-*tritoluene*-p-*sulphonyl* derivative was also obtained, both derivatives being useful for the characterisation of the glycoside. α-Ethyl-2 : 3-dideoxy-D-glucoside was prepared according to Laland, Overend, and Stacey (*J.*, 1950, 738). It was non-reducing to lead tetra-acetate, showing that it had a pyranose structure, and yielded a crystalline 4 : 6-*di*-p-*nitrobenzoate*.

The various glycosides described were treated with acid and their rates of hydrolysis were followed polarimetrically. Fig. 5 illustrates the results obtained. Equimolecular solutions were used for the experiments and, since the glycoside concentration in solution was low, the

hydrolytic reaction was assumed to be of the first order, and the results are represented as percentages of hydrolysis based on the initial and final rotations obtained. From the data recorded, and from comparisons with the work of Overend, Stacey, and Staněk (*loc. cit.*) it seems that the glycosides of 2-deoxy-hexoses are more stable than those of the corresponding deoxy-pentoses (cf. Hirst, *J.*, 1949, 522) and that, as in the normal sugar series, glycofuranosides are

FIG. 5.



I. α-*Ethyl*-D-*glucofuranoside* 5 : 6-*carbonate* (*scale A*).
II. α-*Ethyl*-2 : 3-*dideoxy*-D-*glucoside* (*scale A*).
III. *and* IV. α- *and* β-*Ethyl*-D-*glucopyranoside* (*scale B*).
V. *Ethyl* 2-*deoxy*-D-*glucoside* (*scale B*).

much more labile than glycopyranosides. Moreover, an increase in the number of deoxy-groups in the sugar chain definitely increases the lability of glycosidic residues to acid. For example, α-ethyl-2 : 3-dideoxy-D-glucopyranoside is more labile to acid than is α-ethyl-2-deoxy-D-glucopyranoside. So far we have been unsuccessful in our attempts to prepare α- or β-ethyl-2 : 3-dideoxy-D-glucofuranoside, no doubt because of its extreme lability. Finally it appears that the ethylglycosides of 2-deoxy-sugars are somewhat more stable than the corresponding methylglycosides.

EXPERIMENTAL.

2-Deoxy-D-glucose Anilide.—(*a*) An alcoholic solution of aniline (0·1 c.c. in 1 c.c.) was added to an aqueous solution of 2-deoxy-D-glucose (0·1 g. in 5 c.c.) which had been treated with 0·01N-sulphuric acid until it was just acid to Congo-red. The mixture was shaken at room temperature for 10 minutes and then left at 0° for 24 hours. Needle-shaped crystals separated and were collected. After recrystallisation from ethanol, the anilide was obtained as colourless needles (0·06 g., 43%), m. p. 188—189°. If the addition of sulphuric acid to the solution of the deoxy-sugar was omitted an increased yield (70%) was obtained (Overend, Stacey, and Staněk, *J.*, 1949, 2841, quote m. p. 193—194° for this compound).

(*b*) 2-Deoxy-D-glucose (0·1 g.) in ethanol (12 c.c.) containing water (1 c.c.) was heated under reflux with aniline (0·1 g.) for 2 hours. A slight brown residue was removed, and on storage crystals separated and were collected. Concentration of the mother-liquors yielded a further crop of crystals. These were recrystallised from ethanol, and the anilide (0·09 g., 64%) was obtained as colourless needles, m. p. 193—194°. The m. p. on admixture with the product of (*a*) was 188—189° (Found: C, 60·3; H, 7·1; N, 5·6. Calc. for $C_{12}H_{17}O_4N$: C, 60·2; H, 7·1; N, 5·9%). The product was soluble in hot water and slightly soluble in hot acetone. It showed mutarotational changes as follows: $[\alpha]_D$ −153° (5 minutes) ⟶ −102° (19 hours) (*c*, 1·0 in pyridine); $[\alpha]_D$ −64° (20 minutes) ⟶ −60° (approx.) (4 hours) (in methanol). Attempts to acetylate 2-deoxy-D-glucose anilide with acetic anhydride in dry pyridine at 0° for 4 days yielded only syrupy mixtures. When the anilide (0·08 g.) prepared by method (*a*) in solution in absolute ethanol (20 c.c.) was heated under reflux for 4 hours it underwent no change.

De-anilination of 2-Deoxy-D-glucose Anilide.—2-Deoxy-D-glucose anilide (0·08 g.) was treated with 0·5% formic acid (20 c.c.) at 80° for 1 hour. The mixture was steam-distilled and then neutralised with lead carbonate. After filtration the neutral solution was concentrated to dryness under diminished pressure. The residue was extracted with 95% ethanol and filtered, and then hydrogen sulphide was passed through the solution. After filtration through a charcoal pad the solution was evaporated to dryness. Nucleation with 2-deoxy-D-glucose and trituration with ethanol induced the syrupy residue to crystallise. The crystals were washed with ethanol and dried (13 mg.), m. p. 142° alone or on admixture with authentic 2-deoxy-D-glucose.

2-Deoxy-D-galactose Anilide.—A suspension of 2-deoxy-D-galactose (0·4 g.) in aniline (0·5 c.c.) and ethanol (10 c.c.) was heated under reflux for 1 hour. The sugar gradually dissolved. Concentration of

the solution yielded a syrup which crystallised. The crystals (0·4 g., 60%) were collected, washed with absolute ethanol, and dried. *2-Deoxy-D-galactose anilide* had m. p. 134—135° (decomp.), $[\alpha]_D^{25}$ −116° (initial) ⟶ −53° when catalysed with 1 drop of 0·1N-H_2SO_4 (*c*, 1·3 in methanol) (Found: C, 59·9; H, 7·4; N, 5·4. $C_{12}H_{17}O_4N$ requires C, 60·2; H, 7·1; N, 5·9%). Acetylation of the anilide with acetic anhydride in pyridine afforded only syrupy materials.

2-Deoxy-L-ribose Anilide.—(*a*) A solution of 2-deoxy-L-ribose (0·1 g.) in water (2 c.c.) was added to aniline (0·1 c.c.) in ethanol (5 c.c.). The mixture was kept at 0° for 18 hours. Crystals separated and were collected. After being washed with ice-cold absolute ethanol and dried, the anilide (0·1 g., 68%) had m. p. 172—173° (Deriaz *et al.*, *J.*, 1949, 1879, give m. p. 169·5—170·5°).

(*b*) A suspension of 2-deoxy-L-ribose (0·14 g.) in absolute ethanol (5 c.c.) was boiled under reflux with aniline (0·11 g.) in ethanol (5 c.c.) until complete dissolution was effected (3 hours). Concentration of the solution yielded the anilide (0·19 g., 90%), m. p. 174—175° [on admixture with the product from method (*a*), 172—173°], $[\alpha]_D$ −142° (10 minutes) ⟶ −58° (240 minutes) (*c*, 1·0 in dry pyridine), $[\alpha]_D$ −73° (16 minutes) ⟶ −6·6° (20 hours) (*c*, 0·4 in methanol).

2-Deoxy-D-xylose Anilide.—This was prepared according to Overend, Shafizadeh, and Stacey (*J.*, 1950, 1027).

D-Glucose Anilide.—This anilide was prepared from D-glucose and aniline by the usual procedure (Cameron, *J. Amer. Chem. Soc.*, 1926, **48**, 2233), and had m. p. 142—143° (decomp.), $[\alpha]_D^{25}$ +1·7° ⟶ −48·1° when catalysed with 2 drops of 0·1N-sulphuric acid (*c*, 1·2 in methanol) (Cameron, *loc. cit.*, gives m. p. 140—147° (decomp.) and $[\alpha]_D$ −52° in methanol).

D-Galactose Anilide.—This sample, prepared according to Butler, Smith, and Stacey (*J.*, 1949, 3371), had m. p. 146—148° (decomp.), $[\alpha]_D$ −112° (15 minutes) ⟶ −56° (24 hours) (*c*, 1·1 in pyridine), −92° (1·5 hours) ⟶ −37° (92 hours) (*c*, 1·2 in methanol).

D-Ribopyranose Anilide.—This was prepared according to Lee and Berger (*J. Org. Chem.*, 1946, **11**, 75) in 83% yield and had m. p. 114—116° (sintering 112—114°), $[\alpha]_D$ +62° (3 minutes) ⟶ +60° (24 hours) (*c*, 1·0 in pyridine), +23° ⟶ +13° (17 hours) (*c*, 1·0 in methanol). Lee and Berger (*loc. cit.*) give m. p. 125—127° and $[\alpha]_D^{25}$ +63·4° ⟶ +48·6° in 48 hours (*c*, 1·0 in pyridine). Howard, Kenner, Lythgoe, and Todd (*J.*, 1946, 855) give m. p. 119°, $[\alpha]_D^{17}$ +60° constant during 30 hours (*c*, 0·95 in dry pyridine), +60° (initial value) ⟶ +48·4° (final value after 2 days) (*c*, 0·95 in moist pyridine), $[\alpha]_D^{20}$ +71° (initial value) ⟶ +43° (final value after 4½ hours) (*c*, 0·75 in pyridine containing 10% of acetic acid).

D-Ribofuranose Anilide.—In like manner this compound was obtained in 70% yield after Lee and Berger's (*loc. cit.*) instructions, and had m. p. 123—124°, $[\alpha]_D$ +182° (4 minutes) ⟶ +52·3° (22 hours) (*c*, 2·0 in pyridine), +135° (13 minutes) ⟶ +12° (47 hours) (*c*, 1·0 in methanol). Lee and Berger give m. p. 138—140° and $[\alpha]_D^{25}$ +176·5° ⟶ +156·6° (24 hours) (*c*, 3·0 in pyridine). Howard, Kenner, Lythgoe, and Todd (*loc. cit.*) give m. p. 126—127°, $[\alpha]_D^{17}$ +180° constant during 30 hours (*c*, 0·85 in dry pyridine), $[\alpha]_D^{20}$ +176° (initial value) ⟶ +161° (final value after 3 days) (*c*, 0·85 in moist pyridine), $[\alpha]_D^{20}$ +176° (initial value) ⟶ +44° (final value after 2·5 hours) (*c*, 1·11 in pyridine containing 10% of acetic acid). It is the view of Lee and Berger (*loc. cit.*) that the m. p.s of ribose anilides are not critical but vary with the conditions of isolation of the derivatives.

D-Xylose Anilide.—A suspension of D-xylose (2 g.) in methanol (15 c.c.) was heated under reflux with aniline (2·4 c.c.) for 3 hours. The clear yellow solution was concentrated to small bulk, whereupon crystals separated. Recrystallisation from methanol gave D-xylose anilide (0·317 g.), m. p. 142—144° (decomp.), $[\alpha]_D^{25}$ −90° (5 minutes) ⟶ −48° (46 hours) (*c*, 1·0 in methanol) (Found: C, 58·9; H, 6·5. Calc. for $C_{11}H_{15}O_4N$: C, 58·7; H, 6·6%). Howard, Kenner, Lythgoe, and Todd (*loc. cit.*) give m. p. 142°, $[\alpha]_D^{25}$ −87° (*c*, 2·37 in pyridine).

Optical Rotations of Galactose, Glucose, and Ribose in Methanol or Aqueous Methanol in the Presence of Sulphuric Acid.—(*a*) *Anhydrous* α-D-*galactose.* 0·983N-Sulphuric acid (1·1 c.c.) was added to a solution of anhydrous α-galactose in aqueous methanol (4 : 1) (10 c.c.) (*c*, 1·0; 0·0052 mols./100 c.c. of solvent), and the change in optical rotation was observed.

Time (mins.)	1	2	4	5	8	13	18	107
$[\alpha]_D^{25}$	+110°	+103°	+95·5°	+89·8°	+84·2°	+78·6°	+77·4°	+74·1°

(*b*) *Anhydrous* α-D-*glucose.* 0·983N-Sulphuric acid was added to a solution of anhydrous α-glucose in aqueous methanol (13 c.c. of methanol; 1 c.c. of water) (10 c.c.) (*c*, 1·3; 0·0042 mol./100 c.c. of solvent). Changes in optical rotation were:

Time (mins.)	1	3	5	10	16	35	100
$[\alpha]_D^{25}$	+104°	+96·5°	+88°	+79·9°	+73·1°	+64·3°	+62·8°

(*c*) D-Ribose. When 0·983N-sulphuric acid (1 c.c.) was added to a solution of ribose in absolute methanol (10 c.c.) (*c*, 0·7; 0·0047 mol./100 c.c. of methanol) there was an immediate change in the specific rotation from −17° to −25°. This value then remained constant for 1 hour.

Hydrolysis of Anilides.—The general procedure adopted was to add either N- or 0·1N-sulphuric acid (1 c.c.) to an equilibrated solution, in methanol (10 c.c.), of the sugar anilide (*c*, 0·044 mol./l.) (N.B. for 2-deoxy-D-glucose and 2-deoxy-D-ribose this concentration was found to exceed the maximum solubility in the solvent, and so for these derivatives saturated solutions were used). The ensuing reactions were followed polarimetrically. Results are indicated in Figs. 1—4. Times taken for the various solutions to reach a constant value for the optical rotation are as follows:

Sugar anilide.	Time, mins. (N-H_2SO_4).	Sugar anilide.	Time, mins. (N-H_2SO_4).	Sugar anilide.	Time, mins. (N-H_2SO_4).
2-Deoxy-D-xylose ...	15	2-Deoxy-D-glucose	18	D-Galactose	80
2-Deoxy-L-ribose ...	3	D-Ribofuranose	120	D-Glucose	600
2-Deoxy-D-galactose	8	D-Ribopyranose ...	140	D-Xylose	80

β-Ethyl-D-glucopyranoside.—This was prepared in the usual manner (Ferguson, *J. Amer. Chem. Soc.*, 1932, **54**, 4066) and recrystallised from ethyl acetate–acetone as hygroscopic needles, m. p. 98—100°, $[\alpha]_D^{15}$ −37·9° (*c*, 1·84 in water). Ferguson (*loc. cit.*) gives m. p. 90·4° and $[\alpha]_D$ −36·4° in water. It formed a crystalline tetra-acetate, m. p. 106°, and *tetra-p-nitrobenzoate*, m. p. 215—216°, $[\alpha]_D^{15}$ +28° (*c*, 0·71 in acetone) (Found: C, 53·9; H, 3·0; N, 7·0. $C_{48}H_{44}O_{18}N_4$ requires C, 53·7; H, 3·5; N, 7·0%).

α-Ethyl-D-glucopyranoside.—This was prepared according to Fischer (*Ber.*, 1895, **28**, 1154). When treated with *p*-nitrobenzoyl chloride in pyridine it afforded a crystalline *tetra-p-nitrobenzoate*, which, after recrystallisation from ethanol–acetone, had m. p. 110—115° (Found: C, 53·4; H, 3·4; N, 6·8%).

α-Ethyl-D-glucofuranoside 5:6-Carbonate.—The ethyl glucofuranoside 5:6-carbonate, prepared from 1:2-isopropylidene-D-glucose 5:6-carbonate by the method of Haworth and Porter (*J.*, 1929, 2796), had m. p. 131—132°.

Ethyl-2-deoxy-D-glucopyranoside.—(a) *From 2-deoxy-D-glucose.* Small-scale trial experiments showed that 0·2% ethanolic hydrogen chloride was most suitable for the glycosidation. 2-Deoxy-D-glucose (100 mg.) was dissolved in dry ethanol (8·5 c.c.) to which was added 3·49% ethanolic hydrogen chloride (0·53 c.c.). The solution was kept at room temperature and the reaction was followed polarimetrically. After 24 hours the solution was neutralised with silver carbonate and filtered through charcoal, and the filtrate evaporated to dryness under diminished pressure. The residue crystallised and was recrystallised from ethyl acetate. *Ethyl-2-deoxy-D-glucoside* (60 mg.) was obtained as colourless prisms, m. p. 122—123°, $[\alpha]_D^{15}$ +120° (*c*, 1·1 in water) (Found: C, 49·6; H, 8·3; OEt, 23·1. $C_8H_{16}O_5$ requires C, 49·97; H, 8·4; OEt, 23·4%).

(b) *From D-glucal.* D-Glucal (2·92 g.), dried *in vacuo* over phosphoric oxide, was dissolved in 1·6% ethanolic hydrogen chloride (31 g.). After 5 hours at room temperature the solution was neutralised with silver carbonate, and the crude product isolated in the usual manner. This oily product partly crystallised and the crystals were separated and washed with ether. After recrystallisation from ethyl acetate, ethyl-2-deoxy-D-glucoside, m. p. 121—122°, was obtained (0·16 g.) identical with the product described above. In addition oily material (0·43 g.) was obtained, b. p. 100—130° (bath temp.)/0·005 mm., which is not yet identified (Found: C, 57·6; H, 7·3%).

Hydrolysis of Ethyl-2-deoxy-D-glucoside.—Ethyl 2-deoxy-D-glucoside (60 mg.) was dissolved in N-hydrochloric acid (5 c.c.), and the solution was kept at room temperature for 48 hours. The solution was neutralised (silver carbonate) and then filtered and the filtrate evaporated at room temperature in a vacuum-desiccator over phosphoric oxide or sulphuric acid. The syrupy residue partly crystallised and was treated with concentrated hydrochloric acid (2 vols.) and toluene-ω-thiol (2 vols.). The mixture was shaken for one hour and then diluted with water. The precipitate formed was filtered off, washed with water, and recrystallised from 70% ethanol. 2-Deoxy-D-glucose dibenzyl mercaptal (35 mg.) was obtained, m. p. 153—154° alone or on admixture with the product described by Overend, Stacey, and Staněk (*J.*, 1949, 2841).

Oxidations of Ethyl-2-deoxy-D-glucoside.—(a) *By lead tetra-acetate.* Ethyl-2-deoxy-D-glucoside (52·1 mg.) was added to a solution of lead tetra-acetate in acetic acid. The reaction was followed titrimetrically (Hockett and McClenahan, *J. Amer. Chem. Soc.*, 1939, **61**, 1667).

Time (hours)	0	0·5	1·2	2	3	5	7	8	9	20
Mole of $Pb(OAc)_4$ consumed	0	0·055	0·074	0·11	0·148	0·260	0·52	0·63	0·63	0·90

(b) *By sodium metaperiodate* (cf. Reeves, *J. Amer. Chem. Soc.*, 1941, **63**, 1476). From the oxidation of ethyl-2-deoxy-D-glucoside (10 mg.) by sodium metaperiodate no formaldehyde–dimedon complex could be isolated.

3:4:6-Tri-p-nitrobenzoyl Ethyl-2-deoxy-D-glucoside.—Ethyl-2-deoxy-D-glucoside (50 mg.) was added to *p*-nitrobenzoyl chloride (250 mg.) in pyridine (0·2 c.c.). The mixture was kept at room temperature for 20 hours and the product was isolated in the usual manner. The *3:4:6-tri-p-nitrobenzoate* (70 mg.) was recrystallised from 96% ethanol as colourless nodules, m. p. 140—142°, $[\alpha]_D^{15}$ +72·5° (*c*, 1·2 in benzene) (Found: C, 54·4; H, 3·5. $C_{39}H_{26}O_{14}N_3$ requires C, 54·5; H, 3·7%).

3:4:6-Tritoluene-p-sulphonyl Ethyl-2-deoxy-D-glucoside.—Ethyl-2-deoxy-D-glucoside (32 mg.) and toluene-*p*-sulphonyl chloride (110 mg.) were added to dry pyridine (1 c.c.). The resulting mixture was kept at room temperature for 24 hours and then poured into water. The insoluble material was collected and recrystallised from 96% ethanol. The *3:4:6-tritoluene-p-sulphonate* was obtained as colourless needles, m. p. 100—101°, $[\alpha]_D^{15}$ +83° (*c*, 0·44 in benzene) (Found: C, 53·2; H, 5·3. $C_{39}H_{44}O_{11}S_3$ requires C, 53·2; H, 5·2%).

α-Ethyl-2:3-dideoxy-D-glucopyranoside.—This was prepared according to Laland, Overend, and Stacey (*J.*, 1950, 738) by the catalytic hydrogenation of α-ethyl-2:3-didehydro-2:3-dideoxy-D-glucoside. It had m. p. 67—69° and $[\alpha]_D^{15}$ +140·6° (*c*, 0·69 in water) (Found: C, 54·4; H, 9·0. Calc. for $C_8H_{16}O_4$: C, 54·5; H, 9·1%). It was non-reducing to lead tetra-acetate solution in acetic acid.

4:6-Di-p-nitrobenzoyl α-Ethyl-2:3-dideoxy-D-glucoside.—The glucoside (50 mg.) and a solution of *p*-nitrobenzoyl chloride (130 mg.) in dry pyridine (0·2 c.c.) were kept together for 20 hours at room temperature. The mixture was poured into water, and the product isolated in the usual manner. After recrystallisation from ethanol, the *di-p-nitrobenzoate* (75 mg.) was obtained as colourless needles, m. p. 131·5—132·5°, $[\alpha]_D^{15}$ +109° (*c*, 1·35 in benzene) (Found: C, 55·6; H, 4·6; N, 5·8. $C_{28}H_{22}O_{12}N_2$ requires C, 55·7; H, 4·7; N, 5·9%).

Rates of Hydrolysis.—The hydrolysis of α- and β-ethyl-D-glucofuranoside, α-ethyl-D-glucofuranoside 5:6-carbonate, α-ethyl-2:3-dideoxy-D-glucoside, and ethyl-2-deoxy-D-glucoside by N-hydrochloric acid (*c*, 1·2) at 18° was followed polarimetrically.

(*a*) α- and β-Ethyl-D-glucopyranoside showed no change in optical rotation.

(*b*) α-Ethyl-D-glucofuranoside 5:6-carbonate showed the following changes:

Time (mins.)	5	6	9	12	18	24	30	45	54	74	92	1480
$[\alpha]_D^{15}$	+100°	+98°	+80°	+70°	+60°	+40°	+34°	+24°	+20°	+14°	+10°	+10°

(*c*) With α-ethyl-2 : 3-dideoxy-D-glucoside the changes observed were :

Time (mins.)	3	17	37	58	73	121	161	199
$[\alpha]_D^{20}$	+124°	+96°	+76°	+55·5°	+47°	+36°	+30°	+30°

(*d*) A similar procedure with ethyl-2-deoxy-D-glucoside, gave :

Time (hours)	0	11·5	24·5	48·5	75·5	96·5	125·5
$[\alpha]_D^{20}$	+126°	+106°	+87°	+75°	+57°	+50°	+46·8°

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296. *Syntheses of Neurotropic and Musculotropic Stimulators and Inhibitors. Part III.* Derivatives of Unsaturated ω-Betaines.*

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The Doebner–Knoevenagel reaction with aldehydic quaternary ammonium salts and malonic acid provides a synthesis of unsaturated ω-betaines, including the known trimethyl-(3-carboxyallyl)ammonium chloride (II; R = H, X = Cl) or crotonobetaine hydrochloride. The latter is esterified with the appropriate alcoholic hydrogen chloride, and a new procedure, through the acid chloride obtained by thionyl chloride, is described, yielding the new benzyl, n-amyl, and n-octyl esters, which represent water-soluble derivatives of these alcohols. The acid chloride also yields the amide and carbethoxymethylamide. Trimethyl-(3-carbethoxy-2-ethoxyallyl)ammonium bromide has also been prepared.

Reference is made to pharmacological experiments with some of these compounds.

γ-CROTONOBETAINE (I) has been isolated in small quantities from beef muscle by Linneweh (*Z. physiol. Chem.*, 1928, **175**, 91) who synthesised its hydrochloride (II; R = H, X = Cl) from ethyl γ-chlorocrotonate and trimethylamine (*ibid.*, 1928, **176**, 217), and found that it resembled γ-butyrobetaine in pharmacological effects, which were "curare-like" and weakly parasympathomimetic (*ibid.*, 1929, **181**, 42). According to Strack and Foersterling (*Ber.*, 1938, **71**, 1143; 1943, **76**, 14; *Z. physiol. Chem.*, 1938, **257**, 1; 1942, **277**, 74), who prepared the unsaturated betaine from L-carnitine as described by Engeland (*Ber.*, 1921, **54**, 2208), the parasympathomimetic activity was considerably increased by esterification. Thus, the methyl ester (II; R = Me, X = Cl) showed muscarinic and nicotinic effects which were about one-tenth of those of acetylcholine when tested on muscle preparations. Such relatively high physiological activity of a compound differing biochemically from the neuro-hormone of the parasympathetic nervous system in its resistance to cholinesterase, and, chemically, in that the quaternary ammonium group resides in the acid half of the ester molecule, prompted us to re-examine the synthesis and pharmacological properties of γ-crotonobetaine and related substances some time ago (1942, B.P. 546,596, 546,613, 546,614, and 547,057).

By a Doebner–Knoevenagel reaction with malonic acid and formyltetramethylammonium chloride (III) obtained from trimethylamine and bromoacetal (cf. Berlinerblau, *Ber.*, 1884, **17**, 1139), trimethyl-(3-carboxyallyl)ammonium chloride (γ-crotonobetaine hydrochloride) (II; R = H, X = Cl) has been synthesised. It showed m. p.s ranging from 180° to 199° but, after careful recrystallisation and drying, a deliquescent salt was obtained which decomposed at 200—203° (Linneweh, *loc. cit.*, quotes 203—205°). As the m. p.s of the picrate and chloroplatinate, and of the salt of the corresponding methyl ester (II; R = Me), discussed below, agreed with those given in the literature (Linneweh, *loc. cit.*; Strack and Foersterling, *Ber.*, 1938, *loc. cit.*), there can be little doubt that our compounds were identical with those of the German authors. Observations on the chloroaurate of crotonobetaine which differ somewhat from those in the literature are recorded in the Experimental section. The assignment of αβ- rather than βγ-unsaturation to the products of the present synthesis is based on analogy to a number of examples of the Doebner–Knoevenagel reaction (cf. "Organic Reactions," Vol. I, p. 226). Although it is realised that these comparisons are drawn between products from non-basic and basic aldehydes, the further assumption of the stable crotonic acid configuration is in

* The following papers are to be regarded as Parts I and II, respectively, in this series : *J.*, 1943, 48, 49.

line with the findings of Scheibler and Magasanik (*Ber.*, 1915, **48**, 1810) and von Auwers (*Annalen*, 1923, **432**, 46) that the analogous condensation of acetaldehyde and malonic acid in pyridine leads to crotonic acid and not isocrotonic acid.

$$\underset{\text{(I.)}}{Me_3N^+\cdot CH_2\cdot CH{:}CH\cdot CO_2^-} \qquad \underset{\text{(II.)}}{Me_3\overset{\frown}{N}\cdot CH_2\cdot CH{:}CH\cdot CO_2R} \longleftarrow \underset{\text{(III.)}}{Me_3\overset{\frown}{N}\cdot CH_2\cdot CHO} + CH_2(CO_2H)_2$$
$$\overset{\frown}{X} \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \overset{\frown}{Cl}$$

This method of synthesis has been extended to other aldehydic quaternary ammonium salts. Thus, formylmethyltriethylammonium chloride, obtained by condensation of triethylamine and bromoacetal followed by acid hydrolysis, yielded, with malonic acid, a deliquescent quaternary chloride from which triethyl-(3-carboxyallyl)ammonium reineckate was obtained.

Similarly, trimethyl-(4-carboxybut-3-enyl)ammonium chloride has been synthesised from trimethyl-(2-formylethyl)ammonium chloride which was prepared in a manner similar to that reported by Voet (*Bull. Soc. chim.*, 1929, [iv], **45**, 1016).

In view of the above-mentioned physiological importance of esters of type (II), their preparation was further studied. The methyl ester (II; R = Me), prepared with methanolic hydrogen chloride according to Strack and Foersterling (*Ber.*, 1938, *loc. cit.*), was isolated as reineckate [X = $Cr(CNS)_4(NH_3)_2$], chloride (X = Cl), and sulphate (X = $\frac{1}{2}SO_4$). In an alternative procedure (II; R = H, X = Cl) was treated with thionyl chloride and the resulting crude acid chloride, which could not be readily purified, yielded esters on treatment with alcohols. The methyl ester prepared in this way for the first time yielded the same reineckate and sulphate as were obtained by the methanolic hydrogen chloride route, and the benzyl ester similarly prepared gave trimethyl-(3-carbobenzyloxyallyl)ammonium reineckate, chloride, and iodide [II; R = CH_2Ph, X = $Cr(CNS)_4(NH_3)_2$, Cl, and I, respectively]. That the same ester was obtained by esterification of (II; R = H, X = Cl) with benzyl alcohol and hydrogen chloride was shown by the identity of the characteristic reineckates.

Higher alcohols also react readily with the crude acid chloride product from thionyl chloride, yielding water-soluble esters, analogous to those obtained by Plattner and Geiger (*Helv. Chim. Acta*, 1945, **28**, 1362) from betainyl dichloride.

In this manner the *n*-amyl ester reineckate and sulphate [II; R = *n*-C_5H_{11}, X = $Cr(CNS)_4(NH_3)_2$ and $\frac{1}{2}SO_4$, respectively], and the *n*-octyl ester reineckate were obtained. Conversion of the latter into the corresponding sulphate did not yield a crystalline product; in aqueous solution it behaved as an " inverted " soap, showing marked lowering of surface tension.

Treatment of the crude acid chloride or the methyl ester (II; R = Me, X = Cl), prepared by either method, yielded with ammonia, the corresponding amide which was isolated in the form of reineckate, chloride, and sulphate. The reaction of the acid chloride with ethyl aminoacetate led to the carbethoxymethylamide (II; $NH\cdot CH_2\cdot CO_2Et$ for OR) isolated in the form of its reineckate and deliquescent sulphate. It was of interest at the time to examine this compound for oxytocic activity but practically no effect on the guinea-pig uterus was found. Gulland, Partridge, and Randall (*J.*, 1940, 419) had prepared choline esters of amino-acids and peptides as possible simple analogues of the oxytocic principle of the posterior lobe of the pituitary gland.

Since choline ethers (Dale, *J. Pharm. Exp. Ther.*, 1914, **6**, 147) and trimethyl-(2-methoxyallyl)ammonium bromide (" Esmodil ") (Hecht, *Klin. Woch.*, 1935, **14**, 957) are known to possess strong muscarinic activity, it appeared desirable to synthesise a compound incorporating the alkoxy-group of these two types in a crotonic acid betaine ester.

Accordingly, ethyl γ-bromo-β-ethoxycrotonate (IV), prepared from ethyl β-ethoxycrotonate and *N*-bromoacetamide (Wohl and Jaschinowski, *Ber.*, 1921, **54**, 476), was treated with trimethylamine, yielding trimethyl-(3-carbethoxy-2-ethoxyallyl)ammonium bromide (V).

$$Br\cdot CH_2\cdot \underset{OEt}{C}{:}CH\cdot CO_2Et + Me_3N \longrightarrow \underset{Br}{Me_3\overset{\frown}{N}}\cdot CH_2\cdot \underset{OEt}{C}{:}CH\cdot CO_2Et$$
$$\text{(IV.)} \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \text{(V.)}$$

Preliminary pharmacological tests performed partly by courtesy of the Pharmacological Department of Messrs. F. Hoffmann–La Roche, Basle, and partly by Mr. M. W. Parkes of these laboratories, confirmed the recorded reports as to the parasympathomimetic action of the methyl ester (II; R = Me). The ethoxy-derivative (V), however, showed only weak activity, so that, at least as far as concerns ethoxy- and carbethoxy-groups, the simultaneous presence of the ether and ester groups in the allyl chain tends to abolish acetylcholine-like effect.

A more detailed pharmacological study of the methyl and benzyl esters (II; R = Me and CH_2Ph respectively) has now been reported by Burgen and Hobbiger (*Brit. J. Pharm.*, 1949, **4**, 229).

Experimental.

(M. p.s are uncorrected.)

Formyltrimethylammonium Chloride (III).—*Trimethyl-2 : 2-diethoxyethylammonium bromide* was first prepared by the following convenient procedure as an alternative to that of Fischer (*Ber.*, 1893, **26**, 464) who prepared the iodide by methylation of aminoacetal. A mixture of bromoacetal (25 g.), anhydrous trimethylamine (14 g.), and benzene (25 c.c.) was heated in a sealed tube at 90—100° for 48 hours (cf. Berlinerblau, *Ber.*, 1884, **17**, 1139). After cooling, the crystalline product was collected, washed with dry benzene, and dried (31 g., 95·5%). After crystallisation from alcohol–ether it had m. p. 150—152° (Found : Br, 31·3. $C_9H_{22}O_2NBr$ requires Br, 31·2%). A solution of this bromide (58·7 g.) in water (200 c.c.) was shaken for 30 minutes with moist silver oxide freshly prepared from silver nitrate (43 g.). To the halogen-free filtrate and aqueous washings (total, 325 c.c.) concentrated hydrochloric acid (60 c.c.) was added and the whole boiled under reflux for 20 minutes in a nitrogen atmosphere and evaporated to dryness under reduced pressure. The crystalline residue of *formyltrimethylammonium chloride hydrate* (32·55 g.), washed with dry acetone and dried *in vacuo*, had m. p. 123—124° (Found : Cl, 22·6. $C_4H_{11}ONCl,H_2O$ requires Cl, 22·8%). Fischer (*loc. cit.*) and Berlinerblau (*loc. cit.*) did not give analytical data for their compound but characterised it as chloroplatinate.

Trimethyl(3-carboxyallyl)ammonium Chloride (II; R = H, X = Cl).—A mixture of the above aldehydic salt (15·7 g), malonic acid (15 g.), and dry pyridine (70 c.c.) was heated with stirring on a boiling water-bath for 2 hours. Malonic acid (3 g.) was again added and heating continued for a further hour. Pyridine was removed under reduced pressure and the residue dried by azeotropic distillation with benzene. The product was digested with ethyl acetate, and the crystalline mass dissolved in absolute ethanol (48 c.c.). On cooling to −5° a first crop (8·9 g.; m. p. 190—195°) was obtained and from the mother-liquor a further 2·5 g. (m. p. 190—195°) separated on storage. Recrystallisation from ethanol yielded material which, after careful drying, had m. p. 200—203° (decomp.) (Found : Cl, 19·55. Calc. for $C_7H_{12}O_2NCl$: Cl, 19·8%); the picrate had m. p. 167°, and the chloroplatinate m. p. 223—224° (decomp.). Linneweh (*loc. cit.*) gives 203—205°, 187—189°, and 221—222° (decomp.), respectively.

In some experiments, further crops of the crotonobetaine hydrochloride melted as low as *ca.* 180°. The chloroaurate of this material, however, obtained in nearly theoretical yield had m. p. 202—203° (decomp.) (Found : C, 17·8; H, 2·9; N, 2·8; Au, 40·2. Calc. for $C_7H_{12}O_2N,AuCl_4$: C, 17·4; H, 2·9; N, 2·9; Au, 40·8), whereas the chloroaurate of the first crop, obtained in equal yield, had m. p. 200—201° (decomp.) (Found : C, 17·6; H, 2·6; N, 2·95; Au, 40·3). The mixed m. p. was 204—205°. Engeland (*loc. cit.*) gives 190—195°, and Linneweh (*loc. cit.*) 215—217° for this m. p.

Triethyl-(3-carboxyallyl)ammonium Reineckate.—(Formylmethyl)triethylammonium chloride (1·5 g.), prepared according to Stoermer and Prall (*Ber.*, 1897, **30**, 1504), was heated with malonic acid (1 g.) and dry pyridine (10 c.c.) on a boiling water-bath. Evolution of carbon dioxide was brisk, and heating was continued for 1 hour, with occasional shaking. After removal of the pyridine under reduced pressure the residue was dried over phosphoric oxide, dissolved in absolute ethanol (4 c.c.), and treated with dry ether (8 c.c.). The chloride was thus precipitated as an uncrystallisable oil. It readily yielded a crystalline *reineckate*, m. p. 154—155° (from aqueous acetone) (Found : C, 33·2; H, 5·8; N, 19·0. $C_{14}H_{34}O_2N_5S_4Cr$ requires C, 33·4; H, 5·1; N, 19·5%).

Trimethyl-(4-carboxybut-3-enyl)ammonium Chloride.—3-Chloropropaldehyde diethyl acetal (5 g.) was heated with trimethylamine (3·9 g.) in ethanol (12·5 c.c.) for 15 hours at 100° in a sealed tube (cf. Voet, *Bull. Soc. chim.*, 1929, [iv], **45**, 1016). The solution was concentrated to a small volume under reduced pressure and treated with dry ether which precipitated a light-brown deliquescent solid (3 g.). A solution of this in water (10 c.c.) and concentrated hydrochloric acid (10 c.c.) was left overnight at room temperature in a nitrogen atmosphere to hydrolyse the acetal. Evaporation to dryness *in vacuo* yielded a residue of 2 g. This was heated with malonic acid (2 g.) and dry pyridine (15 c.c.) on a boiling water bath for 3 hours. The mixture was then evaporated under reduced pressure and dried *in vacuo* over phosphoric oxide. The residue was dissolved in a small amount of ethanol and precipitated with dry ether, yielding an oily *chloride* which was converted by digestion with ether into a light-brown deliquescent solid, further purification of which was effected by precipitation from alcoholic solution by dry ether (Found : Cl, 18·3. $C_8H_{14}O_2NCl$ requires Cl, 18·3%). It yielded, by the usual treatment, a reineckate of m. p. 204—207°.

Trimethyl-(3-carbomethoxyallyl)ammonium Salts (II; R = Me).—(*a*) Crotonobetaine hydrochloride (5 g.) was esterified with methanolic hydrogen chloride as described by Strack and Foersterling (*loc. cit.*). It was directly converted into the reineckate (11·1 g.) which formed purple-pink needles, m. p. 159—163°, after recrystallisation from aqueous acetone (Found : C, 30·2; H, 4·5; N, 20·15. Calc. for $C_{15}H_{34}O_2N_5S_4Cr$: C, 30·3; H, 4·6; N, 20·6%).

A solution of the reineckate in acetone–water (1 : 4) was treated with the calculated amount of silver sulphate in aqueous solution, filtered from silver reineckate, and treated with barium chloride solution (cf. Strack and Foersterling, *loc. cit.*). After removal of barium sulphate and complete evaporation under reduced pressure and at low temperature, the residue was crystallised from acetone–methanol, yielding trimethyl-(3-carbomethoxyallyl)ammonium chloride, a deliquescent solid, m. p. 171—174° (decomp.) (Found : Cl, 18·3. Calc. for $C_8H_{14}O_2NCl$: Cl, 18·3%).

A solution of the reineckate (0·447 g.) in acetone–water (3·5 c.c. ; 4 : 1) was treated with a cold aqueous solution of silver sulphate (0·1468 g.; 38 c.c.). The silver reineckate was filtered off and washed with aqueous acetone, and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in methanol, filtered clear, and concentrated to a small volume. Addition of acetone yielded the very deliquescent *trimethyl-(3-carbethoxyallyl)ammonium sulphate*, m. p. 164—165° (decomp.) when anhydrous (Found : C, 46·8; H, 7·4; N, 7·0. $(C_9H_{16}O_2N)_2SO_4$ requires C, 46·5; H, 7·8; N, 6·8%).

(*b*) Crotonobetaine hydrochloride (1 g.) was gently warmed with thionyl chloride (4 c.c.) for 10 minutes on the water-bath. Excess of thionyl chloride was removed at low temperature under

reduced pressure. The residue was triturated with dry ether, but further attempts at purification were unsuccessful. The product (1·1 g.), consisting of the acid chloride, was mixed with absolute methanol (4 c.c.), and the resulting solution boiled for 10 minutes. Methanol (1 c.c.) was again added and boiling continued for a further 5 minutes. After dilution of the cooled solution with ice-water and extraction with ether, the aqueous solution was made slightly alkaline with dilute aqueous ammonia and treated with saturated aqueous ammonium reineckate solution. The precipitated purple-pink reineckate was collected, dried (2·4 g.), and recrystallised by cautious addition of water to a clarified warm acetone solution. It had m. p. 159—161° and was identical with the reineckate described above under (*a*) (mixed m. p. 161—163°) (Found: C, 30·9; H, 4·5; N, 20·4; Cr, 10·2. Calc. for $C_{19}H_{31}O_3N_7S_4Cr$: C, 30·3; H, 4·6; N, 20·6; Cr, 10·9%).

The reineckate was converted into the sulphate as described above, and this material, m. p. 165°, was identical with the sulphate obtained from the methanolic hydrogen chloride esterification (mixed m. p. 164—165°) [Found: C, 46·3; H, 7·4; N, 6·8. Calc. for $(C_9H_{14}O_2N)_2SO_4$: C, 46·5; H, 7·8; N, 6·8%].

Trimethyl-(3-carbobenzyloxyallyl)ammonium Salts (II; R = CH_2Ph).—*Reineckate* [X = $Cr(CNS)_4(NH_3)_2$]. Crotonobetaine hydrochloride (1·42 g.) was converted into the crude acid chloride as already described and this was heated with benzyl alcohol (6 c.c.) for 10 minutes on a boiling water-bath. The dark liquid was cooled and diluted with water, and excess of benzyl alcohol removed by extraction with ether. The aqueous solution, made alkaline to litmus with dilute aqueous ammonia, was treated with a clear solution of ammonium reineckate. The precipitated *reineckate* was collected and dried (4·12 g.) and recrystallised from acetone–water, forming pink needles, m. p. 166—169°. This was identical with the reineckate of the benzyl ester prepared in the following manner (no depression in mixed melting point): Crotonobetaine hydrochloride (1 g.) in benzyl alcohol (4 c.c.) was saturated with dry hydrogen chloride at 0° and the solution kept at room temperature for 16 hours. It was poured into water, and excess of benzyl alcohol was removed and the reineckate prepared as previously (94% yield; m. p. 165—169°) (Found: C, 39·3; H, 5·1; N, 17·5. $C_{19}H_{31}O_3N_7S_4Cr$ requires C, 39·1; H, 4·25; N, 17·7%).

Chloride (X = Cl). A solution of the reineckate in 80% aqueous acetone (30 c.c.) was treated with an aqueous solution of the equivalent amount of silver sulphate. After filtration from silver reineckate, the colourless solution was concentrated to low volume (1/10) under reduced pressure and treated with an aqueous solution of the equivalent amount of barium chloride. After the barium sulphate had settled, the mixture was filtered clear, and the filtrate concentrated under reduced pressure to a syrup which was dried *in vacuo* over phosphoric oxide. The residue was recrystallised from acetone–methanol, yielding the highly hygroscopic cream-coloured *chloride* of low m. p. (45—55°) (Found: Cl, 13·55. $C_{14}H_{20}O_2NCl$ requires Cl, 13·15%).

Iodide (X = I). This *salt*, obtained by treatment of the above chloride in methanol with the equivalent amount of sodium iodide in acetone, had m. p. 149—151° (from methanol) (Found: N, 3·5; I, 35·4. $C_{14}H_{20}O_2NI$ requires N, 3·9; I, 35·2%).

Trimethyl-(3-carbo-n-amyloxyallyl)ammonium Salts (II; R = n-C_5H_{11}).—*Reineckate* [X = $Cr(CNS)_4(NH_3)_2$]. Crude acid chloride of (II; R = H, X = Cl) (0·4 g.) was allowed to react with n-amyl alcohol (1·5 c.c.), and the product converted into the *reineckate* following the procedures already described for analogous esters and their salts. This crystallised from acetone–water in pink felted needles, m. p. 157—158° (Found: C, 36·0; H, 5·5; N, 18·9; Cr, 10·7. $C_{19}H_{35}O_3N_7S_4Cr$ requires C, 36·1; H, 5·6; N, 18·4; Cr, 9·8%).

Sulphate (X = $\frac{1}{2}SO_4$). The reineckate (0·35 g.) yielded, by the usual treatment with silver sulphate, the neutral *sulphate* (0·06 g.), m. p. 177° (from methanol) [Found: N, 5·15; SO_4'', 13·8. $(C_{19}H_{36}O_2N)_2SO_4$ requires N, 5·3; SO_4'', 13·3%].

Trimethyl-(3-carbo-n-octyloxyallyl)ammonium Reineckate [II; R = n-C_8H_{17}, X = $Cr(CNS)_4(NH_3)_2$].—Crude acid chloride of (II; R = H, X = Cl) (0·4 g.) was allowed to react with n-octyl alcohol (1·5 c.c.) at 80° for 45 minutes. By the appropriate procedure the *reineckate* was obtained and recrystallised from acetone–water, m. p. 156—160° (0·21 g.) (Found: C, 39·7; H, 6·2; N, 17·1; Cr, 9·8. $C_{23}H_{44}O_3N_7S_4Cr$ requires C, 39·8; H, 5·8; N, 17·1; Cr, 9·1%).

When the reineckate was decomposed with silver sulphate solution, the resulting aqueous solution of the sulphate showed the properties of soap solution, and the residue, on evaporation, had the appearance of petroleum jelly.

Trimethyl-(3-carbamylallyl)ammonium Salts (II; NH_2 or OR).—(*a*) Crude acid chloride prepared from crotonobetaine hydrochloride (3 g.) was added in small portions to an excess of aqueous ammonia (*d* 0·880) at 0°. Excess of ammonia was removed by evaporation under reduced pressure at 35° to half volume. Ammonium reineckate was added, precipitating the *reineckate* (5·36 g.), which recrystallised from acetone–water in pink needles, m. p. 174—178° (Found: C, 28·6; H, 5·0. $C_{11}H_{21}ON_8S_4Cr$ requires C, 28·6; H, 4·6%).

(*b*) The methyl ester (II; R = Me, X = Cl) (0·4 g.), prepared by the thionyl chloride route, was dissolved in aqueous ammonia (5 c.c.; *d* 0·880). The solution was freed from ammonia and evaporated in a desiccator. An aqueous solution of the residue yielded the reineckate, m. p. 173—175° (0·6 g.), described in (*a*). This was transformed in the usual way into the *sulphate*, m. p. 203—205° (decomp.). Although analysis of this was not entirely satisfactory [Found: C, 41·9; H, 8·3; N, 13·1 (micro-Dumas), 15·1 (micro-Kjeldahl); SO_4'', 24·2. $(C_7H_{14}ON_2)_2SO_4.H_2O$ requires C, 42·0; H, 8·0; N, 14·0; SO_4'', 24·5%], the material could be reconverted into the reineckate identical with the starting material (Found: C, 28·1; H, 4·7; N, 24·9; Cr, 12·6. Calc. for $C_{11}H_{21}ON_8S_4Cr$: C, 28·6; H, 4·6; N, 24·3; Cr, 11·3%).

The methyl ester (II; R = Me, X = Cl) prepared from crotonobetaine hydrochloride (1 g.) with methanolic hydrogen chloride was treated with excess of concentrated ammonia solution, and the solution evaporated after 1½ hours. The residue was purified from alcohol–ether, yielding the quaternary *chloride* of the amide as a highly deliquescent cream-coloured solid (Found: N, 15·3. $C_7H_{14}ON_2Cl$ requires N, 15·7%). This chloride also yielded the reineckate, m. p. 174—177°, described above.

Trimethyl-[3-(carbethoxymethylcarbamyl)allyl]ammonium Salts (II; NH·CH_2·CO_2Et for OR).—The crude acid chloride derived from crotonobetaine hydrochloride (1·77 g.) was mixed with finely powdered silica, the granular product thus obtained was added portion-wise during 15 minutes to a stirred solution of glycine ethyl ester (3·9 g.) in dry ether (30 c.c.) at 0°, and stirring was continued at this temperature for half an hour. The solid was filtered off, washed with dry ether, and digested with cold water (100 c.c.). The aqueous extract was filtered clear, made alkaline to litmus with dilute aqueous ammonia, and treated with an aqueous solution of ammonium reineckate. The pink precipitate was collected, washed with water, alcohol, and ether, and dried (2·7 g.). Recrystallisation from acetone–water yielded the *reineckate*, m. p. 155—158° (Found: C, 30·7; H, 5·0; N, 20·7; Cr, 10·8. $C_{15}H_{31}O_2N_9S_4Cr$ requires C, 32·9; H, 5·0; N, 20·5; Cr, 9·5%).

An 80% aqueous-acetone solution of this reineckate (2·4 g.) was treated with silver sulphate in the manner already described for conversion into the *sulphate* which was isolated by complete evaporation of the aqueous solution obtained, and reprecipitation of the residue from alcohol by ether. Yield: 0·8 g. of highly deliquescent yellow powder, melting range 90—100° [Found: N, 10·5; SO_4'', 16·0. $(C_{11}H_{21}O_2N_2)_2SO_4$ requires N, 10·1; SO_4'', 17·3%]. It is readily reconverted into the original reineckate in the usual manner, m. p. and mixed m. p. 155—158°.

Trimethyl-(3-carbethoxy-2-ethoxyallyl)ammonium Bromide and Reineckate.—Ethyl γ-bromo-β-ethoxycrotonate (Wohl and Jaschinowski, *loc. cit.*) (2·4 g.) was added to a solution of anhydrous trimethylamine (3·5 g.) in a mixture (24 c.c.) of equal parts of benzene and light petroleum (b. p. 60—80°) in a pressure-bottle and kept at room temperature overnight. The crystalline solid which had separated (2·4 g.) was then recrystallised from acetone–ethyl acetate, giving the desired *bromide*, colourless prisms, m. p. 154—156° (Found: Br, 27·05. $C_{11}H_{22}O_3NBr$ requires Br, 27·0%).

An aqueous solution of this salt deposited the *reineckate* on treatment with ammonium reineckate in the usual way. This formed purple-pink crystals (from acetone–water), m. p. 162—164° (Found: C, 33·0; H, 5·05; N, 17·7. $C_{15}H_{33}O_3N_9S_4Cr$ requires C, 33·7; H, 5·25; N, 19·35%).

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297. *Quantitative Studies of the Reactivities of Mixed Carboxylic Anhydrides. Part I. The Composition of the Acylation Products in the Reaction between Acetic Chloroacetic Anhydride and Primary Aromatic Amines.*

By A. R. EMERY and V. GOLD.

The compositions of the products obtained by interaction of acetic chloroacetic anhydride and two primary aromatic amines in a series of solvent mixtures have been determined. In benzene solution the reaction leads mainly (86%) to a chloroacetyl derivative, but the product contains progressively larger amounts of the acetyl derivative as more polar solvents are employed; in 50% acetone–water 72% of the product is the acetanilide. Possible interpretations of these observations are suggested.

MIXED carboxylic anhydrides have been known for nearly a century. Gerhardt (*Annalen*, 1852, **82**, 132; 1852, **83**, 112) prepared them by a modification of Williamson's mixed ether synthesis (*Annalen*, 1852, **81**, 73) (action of an acyl halide on the anhydrous metal salt of another carboxylic acid) and, in spite of its drawbacks, this remains still the most generally applicable method. At the time of their discovery topical interest in mixed anhydrides was provided by their support for a combination of the "radical" and "type" theories (cf. Chiozza, *Annalen*, 1852, **84**, 102; 1854, **91**, 102). Much later their very existence was doubted by Rousset (*Bull. Soc. chim.*, 1895, **13**, 330) who demonstrated their extremely low thermal stability, but it was nevertheless convincingly established, largely through the work of Autenrieth and his collaborators (*Ber.*, 1887, **20**, 3187; 1901, **34**, 168; 1924, **57**, 423, 1002) and Béhal (*Compt. rend.*, 1899, **128**, 1460; 1899, **129**, 681; *Ann. Chim. Phys.*, 1900, **19**, 274; 1900, **20**, 411).

Several investigators have also studied the nature of the product formed when a mixed anhydride is allowed to react with an amine (or alcohol). There are two conceivable reactions:

$$R{\cdot}CO{\cdot}O{\cdot}CO{\cdot}R' + R''{\cdot}NH_2 \longrightarrow R''{\cdot}NH{\cdot}CO{\cdot}R + R'{\cdot}CO_2H$$

or

$$R{\cdot}CO{\cdot}O{\cdot}CO{\cdot}R' + R''{\cdot}NH_2 \longrightarrow R''{\cdot}NH{\cdot}CO{\cdot}R' + R{\cdot}CO_2H$$

However, the conclusions of the early workers were contradictory: very often the experimental conditions were inadequately specified; and the purity of the anhydride was often doubtful. The action of heat causes mixed anhydrides to disproportionate into the two symmetrical anhydrides, so that all specimens obtained by distillation at a high temperature must be suspect. The problem is unusually difficult because no *absolute* method of analysis permits an estimate of the amounts of these impurities: an equimolecular mixture of two symmetrical anhydrides is,

in all analytical respects, indistinguishable from a mixed anhydride. *Relative* criteria of purity, such as freezing points, cannot be devised without the existence of data for an analytically pure specimen (see also the Experimental section).

Recent work on mixed anhydrides has been stimulated by the discovery of the reaction between a keten and an acid to give a mixed anhydride (Hurd and Dull, *J. Amer. Chem. Soc.*, 1932, **54**, 3427). As keten is easily prepared, this process, together with the application of high-vacuum distillation, has made it comparatively easy to prepare mixed anhydrides of acetic acid in, probably, a fairly pure condition.

The study of the reactivities of some mixed carboxylic anhydrides, reported in the present group of papers, forms part of an investigation of the mechanism of heterolytic reactions of acid anhydrides. This Part describes product analyses from the acylation of aniline and of 2 : 4-dichloroaniline by acetic chloroacetic anhydride in benzene, acetone–benzene, acetone, and acetone–water.

Experimental.

Keten.—The keten lamp and absorption apparatus were all-Pyrex modifications of those described (Williams and Hurd, *J. Org. Chem.*, 1940, **5**, 122; Dunbar and Bolstad, *ibid.*, 1944, **9**, 219; Bolstad and Dunbar, *Ind. Eng. Chem. Anal.*, 1943, **15**, 498). A detachable filament was made by winding 100 cm. of 30-gauge Nichrome No. 1 wire on a $\frac{1}{4}$" former; it was run at 3·5 amps. Keten was evolved at the rate of approx. 0·1 mole per hour, provided that the filament was renewed after about 6 hours' working.

Acetic Chloroacetic Anhydride.—A slight excess of keten was passed into a saturated solution and suspension of chloroacetic acid in dry benzene. After evaporation under reduced pressure at room temperature the anhydride was distilled (b. p. 27—30°/~ 0·01 mm.). The distillate is a colourless, lachrymatory liquid, f. p. 4·1—4·7°. The hydrolysable chlorine content was 98—102% of theoretical. The ratio, equivs. of acid produced on hydrolysis with cold water/equivs. of Cl^- produced on complete alkaline hydrolysis, was 1·98—2·03 (theoretical value: 2·00). The ratio, equivs. of acid left after reaction of anhydride with dry aniline in the cold/equivs. of Cl^- produced on complete alkaline hydrolysis, was 1·00—1·06 (theoretical value: 1·00); the excess of the experimental over the theoretical value is a sensitive indication of the amount of free acid in the sample. None of these analytical methods distinguishes between the mixed anhydride and an equimolecular mixture of the two derived symmetrical anhydrides. Nevertheless, the final products used in our experiments were probably fairly pure specimens of acetic chloroacetic anhydride for the following reasons taken collectively: (i) The composition of the acylation product indicates that the preparation must have contained > 70% of its weight of the mixed anhydride. (ii) The amount of disproportionation was inappreciable when our material was kept at the temperature of the distillation for a comparable time. As the middle portion of the distillate was uniform and the b. p.s of the two symmetrical anhydrides are 80° apart (at 110 mm.), the product collected must have been either the pure mixed anhydride or—less probably—a ternary azeotropic mixture containing equimolecular amounts of the two symmetrical anhydrides. (iii) Repeated fractional freezing failed to yield a product having a higher freezing point or giving different product composition in its reaction with amines. The cooling curves had a long flat arrest at the f. p., showing the specimens to be either pure substances or eutectic mixtures. (iv) The hydrolysis in acetone–water accurately followed a first-order law, the rate being intermediate between the values for acetic anhydride and chloroacetic anhydride, whereas the velocity coefficients for the hydrolysis of a product containing other anhydrides as impurities would have decreased as the reaction proceeded.

The small amount of acid present in the product, which is formed during unavoidable brief exposures to the atmosphere, was always determined (by treatment with dry aniline in the cold and titration of the acid produced) and an appropriate allowance made in the calculations. The anhydride was stored, for short periods only, under rigorous exclusion of moisture at a temperature below the f. p.

Other Materials.—Acetone, benzene, and aniline were purified, dried, and fractionally distilled. 2 : 4-Dichloroaniline was purified by steam-distillation and recrystallisation.

Freezing Points.—That of acetic chloroacetic anhydride was measured in a completely enclosed cryoscope by means of a calibrated thermocouple protected by a thin glass sheath. The enclosed stirrer was actuated magnetically. Fractional freezing was carried out in the cryoscope, and the freezing points re-determined on the purified fraction.

Conditions for Acylation Experiments.—A weighed amount of mixed anhydride was added to the amine solution at the temperature at the bath (thermostat). The reaction was allowed to go to completion, the time required being checked by independent experiments, and the products then worked up for analysis. All reaction mixtures remained homogeneous throughout the reaction.

Analysis of Acylation Products.—The total amount of acid in the product was titrated with standard alkali, thus giving the fractions of the total reaction proceeding as acylation and as hydrolysis. The organic solvent was then completely removed from the accurately neutralised solution by suction at room temperature, since acetone interferes with the subsequent extraction. Benzene was added to the resulting suspension of amine and anilides in water, and the organic materials were separated from the aqueous solution of the sodium salts. The chlorine content of the aqueous layer corresponds to the amount of chloroacetic acid formed during the reaction and is equivalent to the sum of the amounts of reaction leading to acetylation and hydrolysis. It was determined by hydrolysis with boiling 5% sodium hydroxide solution, followed by potentiometric titration with silver nitrate solution. The organic layer was evaporated to dryness on a water-bath, and the amount of the chlorine in it, which is equivalent to the total amount of chloroacetylation, determined in the same way after hydrolysis with boiling as above. The method of analysis, checked against synthetic mixtures, gave consistent results. No correction was applied for the slight systematic error (the aqueous layer dissolving about 3% of the chloroacetanilide formed).

In view of the startling dependence of the product ratio upon the solvent, the qualitative correctness of the result was confirmed by experiments on the preparative scale and identification of the major reaction product.

In all experiments with aniline the anhydride reacted to give anilides only, and no hydrolysis occurred even in the most aqueous solvent. With 2 : 4-dichloroaniline an appreciable amount of hydrolysis always took place concurrently with anilide formation, and an appropriate allowance was made for this in the calculation of the chloroacylation ratios.

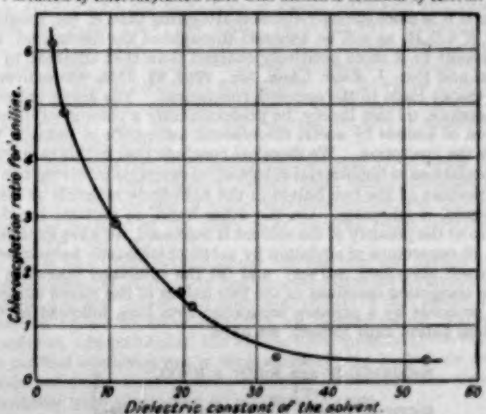
Discussion.

(a) *Experimental Basis.*—The facts which require explanation are given in the Table. They are, briefly: (i) the ratio of chloroacetyl to acetyl derivative (the "chloroacylation ratio") formed in the acylation of aniline with acetic chloroacetic anhydride is a function of the solvent (figure); it decreases from a value > 6 for benzene solution to $\sim 0{\cdot}4$ for 50% aqueous acetone; (ii) the chloroacylation ratio remains virtually unchanged (it decreases by a factor of less than 2) on passing from aniline to 2 : 4-dichloroaniline, although the velocity of the reaction is thereby decreased, probably by a factor of several powers of 10; and (iii) the chloroacylation ratio with 2 : 4-dichloroaniline in 80% acetone–water is only slightly, if at all, dependent on the amine concentration.

The product composition for the acylation of two primary aromatic amines with acetic chloroacetic anhydride in different solvents. $[Cl{\cdot}CH_2{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CH_3]_0 \sim 0{\cdot}06$M.

Expt.	Solvent.	Temperature.	Amine.	$[Amine]_0$.	Chloroacetanilide / Acetanilide (Chloroacylation ratio).
1	Benzene	18°	Aniline	0·6M.	6·1
2	Benzene–acetone (80 : 20 v/v)	,,	,,	,,	4·8
3	Benzene–acetone (50 : 50 v/v)	,,	,,	,,	2·9
4	Acetone	,,	,,	,,	1·6
5	Acetone–water (98 : 2 v/v approx.)	,,	,,	,,	1·3
6	Acetone–water (80 : 20 v/v)	,,	,,	,,	0·44
7	Acetone–water (50 : 50 v/v)	,,	,,	,,	0·39
8	Benzene	25°	2 : 4-Dichloroaniline	0·67	5·5
9	Acetone–water (80 : 20 w/w)	,,	,,	0·148	0·35
10	,, ,,	,,	,,	0·67	0·43; 0·40
11	,, ,,	0°	,,	0·67	0·45

Variation of chloroacylation ratio with dielectric constant of solvent.



It may be remarked that the relative rates of the two acylation reactions are really very similar in all the solvents studied and that the solvent effect only amounts to the reversal of a delicate balance of rates under the influence of a very drastic change of solvent.

(b) *Evidence for Electrophilic Character of the Acylating Agent.*—The acylation of an amine

by means of an acid anhydride or acid chloride is known to be a heterolytic reaction in which the amine behaves as the nucleophilic and the acylating species as the electrophilic reagent. These conclusions follow from the parallelism between the ease of electrophilic nuclear substitution in a substituted benzene and the ease of acylation of the corresponding substituted aniline. Available data refer chiefly to acylation by means of acid chlorides (Williams and Hinshelwood, *J.*, 1934, 1079) but this rule for substituents also holds for the acetylation of substituted anilines with acetic anhydride (Bafna and Gold, unpublished). For acylation with substituted benzoyl chlorides (Williams and Hinshelwood, *loc. cit.*) the effect of substituted groups in the nucleus of benzoyl chloride confirms that reactivity runs parallel with depletion of electrons at the carbonyl-carbon atom which forms the new bond.

An acid anhydride also functions as electrophilic reagent in its reaction with an alcohol, as is indicated by the position of bond fission determined by Dedusenko and Brodskii (*Acta Physicochim.*, 1942, **17**, 314) for the reaction between acetic anhydride and ethyl alcohol. By the use of labelled oxygen in ethyl alcohol it was shown that the oxygen of the alcohol was incorporated in the ester molecule, *i.e.*,

$$CH_3{\cdot}CO|{-}O{\cdot}CO{\cdot}CH_3 + H|{-}O^{18}Et \longrightarrow CH_3{\cdot}CO{\cdot}O^{18}Et + CH_3{\cdot}CO_2H$$

(c) *Molecular Condition of Reagents.*—The molecular state of the amine at the moment of reaction is hardly in doubt. Although some of it will, in the presence of acids, be in the form of an anilinium ion, this form will be very much less reactive than the neutral molecule and is unlikely to participate in the reaction to any appreciable extent; but its presence must be taken into consideration in a detailed kinetic analysis as it reduces the amount of the reactive neutral form.

The state of the acylating agent is not so certain and may vary according to circumstances. For acylation by means of an acid anhydride in the absence of strong acid, the acylating species may be the anhydride molecule itself or an acylium cation $R{\cdot}CO^+$ (Treffers and Hammett, *J. Amer. Chem. Soc.*, 1937, **59**, 1708; Mackenzie and Winter, *Trans. Faraday Soc.*, 1948, **44**, 159, 171, 243; Gold, *ibid.*, p. 506). Such an ionisation is extremely unlikely in benzene solution but must be given serious consideration for the more polar solvents.

(d) *Electronic Considerations regarding the Nature of the Acylation Product.*—If the reactivity of a molecule as an acylating agent is determined by the density of positive charge at the carbon atom of the carbonyl group, then, for the reaction with *molecular* mixed anhydride as reagent, the acylation reaction

$$R{\cdot}CO{\cdot}O{\cdot}CO{\cdot}R' + R''{\cdot}NH_2 \longrightarrow R''{\cdot}NH{\cdot}CO{\cdot}R + R'{\cdot}CO_2H \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (i)$$

should predominate if R is more strongly electron-attracting than R′ (or, roughly, if $R{\cdot}CO_2H$ is a stronger acid than $R'{\cdot}CO_2H$, as will be assumed throughout the discussion), so as to leave the carbonyl group adjacent to R more positively charged than that adjacent to R′ (cf. Hurd and Dull, *loc. cit.*; Hurd and Roe, *J. Amer. Chem. Soc.*, 1939, **61**, 3355, whose oversimplified application of electronic theory leads to the opposite conclusion). The acetic chloroacetic anhydride molecule should therefore, on this theory, be predominantly a chloroacetylating agent.

For the acylation of amines by acetic chloroacetic anhydride in benzene the product composition agrees with the prediction. We therefore conclude that in this case the simplest theory, which regards the acylations as bimolecular substitution reactions involving two neutral molecules and the reaction velocities of the two halves of the anhydride molecule as largely governed by electronic requirements, is adequate. On the other hand, to account for the reversal of the chloroacylation ratio as the polarity of the solvent is increased, we have explored two alternative sets of postulates: (i) occurrence of acylation by acetic chloroacetic anhydride in polar solvents predominantly through acetylium cations; and (ii) the combined operation of solvation and steric factors in the competing reactions of the two halves of the mixed anhydride molecule.

If the reaction proceeds by a primary separation into ions, followed by the attack of the amine by the acylium cation thus formed, we have

$$\left.\begin{aligned} R{\cdot}CO{\cdot}O{\cdot}CO{\cdot}R' &\underset{-1}{\overset{1}{\rightleftharpoons}} R{\cdot}CO^+ + R'{\cdot}CO_2^- \\ R{\cdot}CO^+ + R''{\cdot}NH_2 &\xrightarrow{2} R''{\cdot}NH{\cdot}CO{\cdot}R + H^+ \end{aligned}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (ii)$$

or

$$\left.\begin{aligned} R{\cdot}CO{\cdot}O{\cdot}CO{\cdot}R' &\underset{-1'}{\overset{1'}{\rightleftharpoons}} R'{\cdot}CO^+ + R{\cdot}CO_2^- \\ R'{\cdot}CO^+ + R''{\cdot}NH_2 &\xrightarrow{2'} R''{\cdot}NH{\cdot}CO{\cdot}R' + H^+ \end{aligned}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (ii')$$

For a full analysis it would be necessary to consider as separate possibilities several relationships among the rate constants in the two schemes. Without at this stage reproducing the mathematical details of this mechanism we may qualitatively predict with some confidence that, if $R{\cdot}CO_2H$ is a stronger acid than $R'{\cdot}CO_2H$, the ionisation according to (ii') will proceed more readily (in both a kinetic and a thermodynamic sense) than that according to (ii), so that it will be more probable to find $CH_3{\cdot}CO^+$ ions in solution than $CH_2Cl{\cdot}CO^+$ ions.* Therefore, if acylation occurs *via* an intermediate acylium cation, we would predict acetylation to occur to a larger extent than chloroacetylation. This hypothesis would, therefore, suffice to explain the reversal of the product ratio with increasing ionising power of the solvent, whereupon the ionic mechanism would gradually assume greater importance. We shall show in Parts II and III that kinetic experiments designed to test the correctness of these assumptions do not, however, offer support for this interpretation.

KING'S COLLEGE, LONDON. [*Received, January 24th*, 1950.]

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298. *Quantitative Studies of the Reactivities of Mixed Carboxylic Anhydrides. Part II. The Determination of Some Reaction Velocities involving Acetic Chloroacetic Anhydride.*

By A. R. EMERY and V. GOLD.

The velocity of the hydrolysis of acetic chloroacetic anhydride in acetone–water (80 : 20 w/w) and the influence of added substances upon it have been studied. The chief effect of added acetate or chloroacetate ions seems to be a fairly rapid reaction with the mixed anhydride to give a symmetrical anhydride, the different rate of hydrolysis of which disturbs the first-order nature of the reaction. The results are complex but, on the whole, do not indicate the existence of specific and common-ion intervention by these anions, such as would be expected on the basis of an ionisation reaction mechanism.

The velocities of overall acylation, acetylation, and chloroacetylation of 2 : 4-dichloroaniline have been determined by combining the hydrolysis results with those of competitive acylation–hydrolysis. The effects of added acetate and chloroacetate ions accord with the interpretation of their effect on the hydrolysis velocity.

ALTHOUGH the kinetics of the hydrolysis of symmetrical carboxylic anhydrides, in particular of acetic anhydride, have engaged the attention of a large number of workers, reaction velocities involving mixed anhydrides have been the subject of only two reasonably detailed recorded investigations, both dealing with the hydrolysis of mixed fatty acid anhydrides, mainly acetic propionic anhydride (Verkade, *Rec. Trav. chim.*, 1915, **35**, 299; Kilpatrick and Kilpatrick, *J. Amer. Chem. Soc.*, 1930, **52**, 1418). The main points of interest emerging were: (i) that the reaction is of the first order, thus showing that the substance investigated was homogeneous and not a mixture of the two symmetrical anhydrides; in the latter case the first-order rate coefficients would have decreased with time owing to the different rates of hydrolysis of the two symmetrical anhydrides; and (ii) that the reaction velocity is intermediate between the values for the symmetrical anhydrides.

In the preceding paper two alternative interpretations were given of the drastic effect of the solvent on the proportions of the products formed from acetic chloroacetic anhydride and an aromatic amine. According to one of these, this observation was ascribed to a change of reaction mechanism, the reaction in the more polar solvents being interpreted as proceeding *via* ionisation to $CH_3{\cdot}CO^+$ and $CH_2Cl{\cdot}CO_2^-$.

In the present paper more information about the reaction mechanism in polar solvents is derived from the determination of absolute reaction velocities for hydrolysis, overall acylation of 2 : 4-dichloroaniline, and acetylation and chloroacetylation of that amine, and from the study of the effects of certain anions on these velocities, all measurements relating to 80 : 20 (w/w) acetone–water as solvent. In particular, the kinetic consequences of the ionisation mechanism were tested. The method employed was to determine only the hydrolysis velocity directly and to obtain the other velocities from product analyses of competitive experiments in which hydrolysis and acylation were proceeding at comparable rates.

* These considerations would have to be somewhat modified if the introduction of an acid-strengthening group should nevertheless stabilise the derived acylium cation because of a large polarisability which permits a greater delocalisation of the positive charge. It is, however, improbable that such a state of affairs need be gone into more fully in the present case, as is shown by the base-weakening effect of chlorine substitution in aliphatic and aromatic amines.

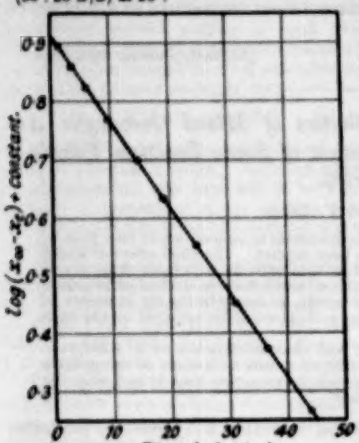
Experimental.

Materials.—Acetic chloroacetic anhydride: see Part I. Acetone–water (80% of acetone by weight) was generally made up from distilled water and AnalaR acetone without further purification, after it had been found that treatment of acetone by the method of Conant and Kirner (*J. Amer. Chem. Soc.*, 1924, **46**, 245) and use of conductivity water did not materially alter the results.

Sodium acetate, potassium acetate, and sodium chloroacetate used were anhydrous salts, the last prepared by nearly neutralising, with cooling, a concentrated solution of chloroacetic acid in water with concentrated sodium hydroxide solution, precipitating the anhydrous salt by addition of a large volume of acetone, washing the solid with dry acetone and benzene, and drying it in a vacuum-desiccator. The salt gave a neutral reaction and contained the theoretical amount of chlorine.

Fig. 1.

Illustration of first-order course of the hydrolysis of acetic chloroacetic anhydride in acetone–water (80 : 20 w/w) at 25°.



Chloroaceto-2 : 4-dichloroanilide was prepared by mixing cold benzene solutions of chloroacetyl chloride and 2 : 4-dichloroaniline and crystallising the precipitated anilide from alcohol. It formed needles, m. p. 101·5° (Found: C, 40·6; H, 2·6; N, 5·9; Cl, 44·6. $C_8H_6ONCl_3$ requires C, 40·4; H, 2·5; N, 5·9; Cl, 44·6%).

Determination of Hydrolysis Velocity.—The progress of the reaction was followed by periodically pipetting samples into an "arresting solution" of aniline in aqueous acetone and titrating the liberated acid with carbonate-free sodium hydroxide solution (cf. Vles, *Rec. Trav. chim.*, 1933, **52**, 909). The anhydride still present in solution reacts practically instantaneously with aniline, liberating one mole of acid per mole of anhydride, the total amount of acid in the sample from this reaction and the hydrolysis being given by

$$x_t = 2(a_0 - a_t) + a_t + f_a$$
$$= 2a_0 - a_t + f_a$$

and $$x_\infty = 2a_0 + f_a$$

where a_0, a_t, a_∞ are the amounts of anhydride in the sample, x_0, x_t, x_∞ are the amounts of acid after treatment with aniline at times $t = 0$, $t = t$, $t = \infty$, and f_a is the amount of free acid in the sample due to the free acid content of the anhydride preparation. For a first-order hydrolysis we get for the rate constant of the reaction

$$k_1 = \frac{1}{t} \ln \frac{(x_\infty - f_a)}{2(x_\infty - x_t)} \quad \ldots \quad (i)$$

The first-order nature of the "spontaneous" hydrolysis is confirmed by (*a*) the linear nature of the graphs of $\log (x_\infty - x_t)$ against t (Fig. 1), from the slopes of which the first-order rate coefficients were usually evaluated and (*b*) the absence of a significant dependence of the rate-coefficients on initial concentration of anhydride. For comparison, the velocity coefficients of the two symmetrical anhydrides were determined in the same manner.

Table I.

Velocity of hydrolysis of acetic chloroacetic anhydride in acetone–water (80 : 20 w/w). $[MA]_0 \sim 0{\cdot}05$M.

Temp.	$k_1 \times 10^4$ (sec.$^{-1}$).*	E.	Frequency factor.
0·1°	1·27	9·9 kcals.	10^4
25·0°	5·76		

* In this and the succeeding paper rate constants are expressed in terms of seconds and moles/l. The symbols k_1 and k_2 are reserved for the experimental velocity coefficients of hydrolysis and acetylation, defined by equations (i) and (vi).

Determination of Velocity of Acylation of 2 : 4-Dichloroaniline by Competition Experiments.—If hydrolysis and acylation proceed competitively the total concentration of acid at the end of the reaction is a measure of the extent of the competing reactions, since the hydrolysis reaction yields *two* moles of acid and acylation *one* mole of acid per mole of anhydride reacting. If [X], [A], and [B] represent, respectively, the concentration of total acid, mixed anhydride, and amine (base) at the times indicated by the suffixes, we get

$$[X]_\infty = 2[A]_0 - ([B]_0 - [B]_\infty) \quad \ldots \quad (ii)$$

and $$[X]_\infty = 2k_1 \int_{t=0}^{t=\infty} [A]dt + k_2 \int_{t=0}^{t=\infty} [A][B]dt \quad \ldots \quad (iii)$$

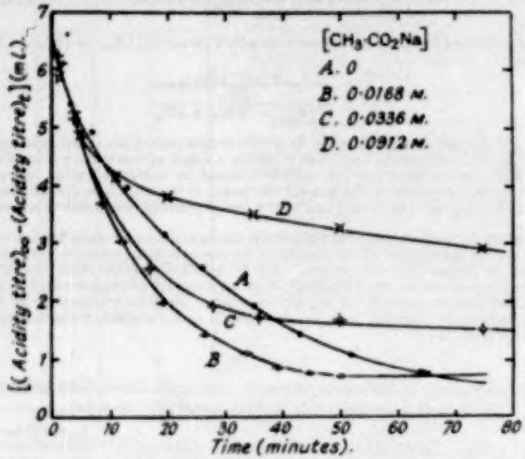
where k_1 and k_2 are the velocity coefficients for hydrolysis and acylation respectively and k, a, and b are undetermined reaction orders. For one set of values of the exponents the expression (iii) becomes equivalent to Wegscheider's test, but it can also be transformed into useful equations for other particular values of k, a, and b. In the present case it seemed reasonable to try an analysis of the experimental data on the assumption that the hydrolysis remains a first-order reaction as before and that the acylation reaction is of the first order with respect to each reaction partner. Then,

$$-\frac{d[A]}{dt} = k_1[A] + k_2[A][B] \quad . \quad . \quad .

disappearance of anhydride upon amine concentration but have carried out a simpler test and shown that, under conditions when the hydrolysis is measurably slow, the addition of aniline to the reaction solution causes the chemical change, which is now exclusively formation of anilide, to be complete when the first measurement is made after 5 minutes; i.e., the presence of amine must have hastened the reaction rate by a factor of the order of 100 at the least. The reaction with aniline cannot, therefore, involve a slow ionisation stage in which the amine does not participate. Since the chloroacylation ratios for aniline and 2 : 4-dichloroaniline are similar it seems plausible to assign the same mechanism to both acylations and not to look on the reaction with aniline as involving molecular anhydride when that with 2 : 4-dichloroaniline does not. Therefore, the partitioning of the acylating agent between water and amine occurs during a slow step, as expressed in the equations (iv) and (v).

FIG. 2.

The effect of sodium acetate addition on the hydrolysis of acetic chloroacetic anhydride.



Solvent: acetone–water (80 : 20 w/w). *Temp.*: 25°. $[MA]_0$ ~0·13M.

By accepting these equations and the validity of (vi), we obtained values for the second-order overall acylation velocity coefficient k_2 by combining the k_1/k_2 values with the result for k_1, from the hydrolysis velocity measurements. The temperature dependence of k_2 leads to a value of approx. 10 kcals. for the activation energy of the overall acylation.

For comparison similar, but less extensive, measurements were carried out for the two symmetrical anhydrides (Table III).

TABLE III.

Comparison of hydrolysis and competition experiments for acetic chloroacetic anhydride and the corresponding symmetrical anhydrides in acetone–water (80 : 20 w/w). Temp. 25°.

Anhydride.	$[A]_0 \times 10^3$.	[2 : 4-Dichloroaniline].	Hydrolysis, %.	k_1/k_2.	$k_1 \times 10^4$.	$k_2 \times 10^4$.
Ac_2O	6·34	0·670	21·5	0·175	5·9	34
$CH_2Cl{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CH_3$	7·95	0·672	54·7	0·77	576	750
$(CH_2Cl{\cdot}CO)_2O$	3·53	0·670	59·3	0·06	6500	6800

Evaluation of Velocity Coefficients for Acetylation and Chloroacetylation of 2 : 4-Dichloroaniline by Acetic Chloroacetic Anhydride.—The second-order acylation velocity coefficients evaluated above are composite, as they are made up of contributions from the acetylation and the chloroacetylation reactions. By determining product ratios as described in Part I, making appropriate allowance for the fact that only part of the anhydride is used up for amine acylation, it is then possible to calculate the velocity coefficients for the constituent reactions, provided that both are of the same kinetic order as the overall reaction, and this seems to be a plausible assumption. The results obtained are given in the last two columns of Table II. The very small temperature dependence of the chloroacylation ratio indicates that acetylation and chloroacetylation by acetic chloroacetic anhydride must have very similar activation energies.

Effect of Added Substances on Velocities.—(a) *Hydrolysis.* Table IV summarises the effect of some substances upon the velocity coefficients whose addition did not disturb the strictly first-order course of the reaction. The effects are small and of the order of magnitude often found as salt or medium effects in heterolytic reactions.

TABLE IV.

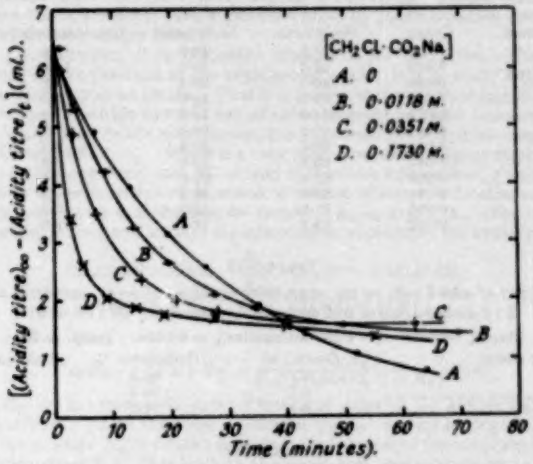
Effect of various substances on the rate of hydrolysis of acetic chloroacetic anhydride in acetone–water (80 : 20 w/w) *at* 25°. $[MA]_0$ ~0·05M.

Substance added.	Concn., M.	$k_1 \times 10^4$.
—	—	5·76
KBr	0·1	6·43
$CH_2Cl{\cdot}CO_2H$	0·1	5·45
H_2SO_4	0·05	6·35

On the other hand, the addition of sodium acetate and sodium chloroacetate had a more pronounced effect on the course of the reaction. This is illustrated by representative curves in Figs. 2 and 3.

FIG. 3.

The effect of sodium chloroacetate addition on the hydrolysis of acetic chloroacetic anhydride.



Solvent: acetone–water (80 : 20 w/w). *Temp.:* 25°. $[MA]_0$ ~0·13M.

Comparative data for the effect of added salts upon the velocity of hydrolysis of acetic anhydride in 50 : 50 (w/w) acetone–water are given in Table V. In these cases there is no corresponding disturbance of the accurate first-order course of the reaction, although sodium acetate and chloroacetate both accelerate the reaction. The change of solvent was dictated by the inconveniently slow hydrolysis of acetic anhydride in 80 : 20 (w/w) acetone–water.

TABLE V.

Effect of added salts on the rate of hydrolysis of acetic anhydride in acetone–water (50 : 50 w/w) *at* 25°. $[Ac_2O]_0$ ~0·07M.

Substance added.	Concn., M.	$k_1 \times 10^3$.
—	—	9·8
KBr	0·1	9·9
CH_3CO_2Na	0·1	25·0
CH_2ClCO_2Na	0·1	20·0

(b) *Competitive experiments.* The results are summarised in Table VI. Owing to the complicated character of the hydrolysis curves it was not possible to analyse the results of the competitive hydrolysis-acylation experiments in the presence of salt by the method described above.

Table VII summarises comparison experiments with acetic anhydride and 2 : 4-dichloroaniline, and Table VIII the effect of added salts upon the chloroacylation ratio for aniline.

It was verified that the α-chloroacetanilides were stable in the presence of acetate ions, therefore, any increase in the experimentally determined content of chloride in the aqueous layer must reflect a genuine change in the proportions of the competing reactions occurring. Before these results are discussed it must also be decided whether the anion effects can be caused by the changed acidity of the

medium. The smallness of the effect of addition of sulphuric acid shows that the change is not due to suppression of acid catalysis. On the other hand, hydrolysis reactions of this kind are very strongly catalysed by OH^- ions (*e.g.*, Ac_2O: Skrabal, *Monatsh.*, 1922, **43**, 493), even in extremely low concentration. To account for our results we would have to assume that there is appreciable hydroxyl-ion catalysis of hydrolysis in acid solutions, since even after addition of sodium acetate or chloroacetate the solutions are definitely acidic after a small amount of reaction has taken place. Such an explanation is finally ruled out (i) by the fact that the course of the hydrolysis is not radically changed if an equivalent amount of acetic acid is introduced in addition to sodium acetate, and (ii) by the strictly first-order course of the " spontaneous " hydrolysis.

TABLE VI.

Effect of added substances in the competitive reactions of acetic chloroacetic anhydride with 2 : 4-dichloroaniline and water in acetone–water (80 : 20 w/w).

$[MA]_0$ ~0·07M. [2 : 4-Dichloroaniline]$_0$ = 0·672M. Temp. = 25·2°.

Added substance.	Concn.	Percentage of total reaction giving Hydrolysis.	Acetylation.	Chloroacetylation.	Chloroacylation ratio.
—	—	51·5	33·9	14·6	0·43
$CH_2Cl{\cdot}CO_2H$	0·102	52·3	30·7	17·0	0·55
$CH_3{\cdot}CO_2H$	0·096	49·0	36·1	14·9	0·41
KBr	0·052	52·8	34·0	13·2	0·39
"	0·076	54·0	32·2	13·8	0·43
"	0·099	60·8	26·5	12·7	0·48
$CH_3{\cdot}CO_2Na$	0·051	60·6	30·2	9·2	0·30
$CH_3{\cdot}CO_2K$	0·081	65·8	28·0	6·2	0·22
"	0·092	67·8	26·8	5·4	0·20
$CH_2Cl{\cdot}CO_2Na$	0·051	66·0	16·7	17·3	1·03
"	0·075	71·2	13·7	15·1	1·10
"	0·102	73·3	12·1	14·6	1·21

TABLE VII.

Effect of added salts on the competitive reactions of acetic anhydride with 2 : 4-dichloroaniline and water in acetone–water (50 : 50 w/w).

$[Ac_2O]_0$ ~0·03M. [2 : 4-Dichloroaniline]$_0$ = 0·185M. Temp. = 25°.

Substance added.	Concn., M.	Hydrolysis, %.	Chloroacetylation, %.
—	—	60·4	—
$CH_3{\cdot}CO_2Na$	0·1	76·4	—
$CH_2Cl{\cdot}CO_2Na$	0·1	71·7	0

TABLE VIII.

Effect of added salts on the chloroacylation ratio for the reaction between acetic chloroacetic anhydride and aniline in acetone–water (80 : 20 w/w).

$[MA]_0$ ~0·03M. [Aniline]$_0$ ~0·7M. Temp. = 25°.

Substance added.	Concn., M.	Chloroacylation ratio.
—	—	0·69
$CH_3{\cdot}CO_2Na$	0·0915	0·75
$CH_2Cl{\cdot}CO_2Na$	0·0989	0·77

DISCUSSION.

(a) *Characteristic Features of an Ionisation Mechanism for Acetylation. Prediction of Common-ion Effect.*—It was suggested in Part I, as *one* interpretation of the observations on the composition of the acylation product and the change of this composition with solvent variation, that acetylation of an aromatic amine by acetic chloroacetic anhydride in aqueous acetone is largely an ionic reaction in which the anhydride molecule ionises to a small extent, according to the scheme:

$$CH_2Cl{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CH_3 \rightleftharpoons CH_3{\cdot}CO^+ + CH_2Cl{\cdot}CO_2^-$$

and that the amine molecule is then attacked by the acetylium cation. Certain peculiarities may be discovered in the reaction kinetics when such a mechanism operates, including a rate-determining stage independent of the nature of the second reactant (in this case the amine) or of common-ion effects. These tests should be applicable to the reactions of acetic chloroacetic anhydride. In view of the negative outcome of these tests we omit the detailed mathematical analysis of the ionisation mechanism and present only an outline of the arguments.

We have shown that the velocity of acylation depends strongly on the nature of the amine used and, therefore, the existence of a common rate-determining stage is ruled out. Furthermore, the chloroacylation ratio does not depend strongly on the nature and concentration of the amine, as it should if one of the acylation reactions occurred by an ionic mechanism. It would, in fact, be unusual for an organic reaction of this type to have an ionic mechanism in which the subsequent reaction of the ion $R{\cdot}CO^+ + R''{\cdot}NH_2 \longrightarrow R''{\cdot}\overset{+}{N}H_2{\cdot}CO{\cdot}R$ is rate-determining and not the initial bond rupture in the anhydride molecule, though the mechanism cannot be entirely dismissed on this argument alone. It follows, however, that if the first stage *is* a rapid equilibrium, then the reaction should always be strongly retarded by the addition of the common anion (in our case, chloroacetate or, possibly, acetate ions). It has not been possible to study the effect of anions on the velocity of amine acetylation. The common-ion effect on acylation should, however, also be noticeable in the chloroacylation ratios, since it should affect the two types of acylation differently. Added acetate and chloroacetate ions were, indeed, found to have a profound effect on chloroacylation ratios, but it could not be explained on such simple lines.

(b) *Kinetic Characteristics of an Ionisation Mechanism for Hydrolysis.*—The hydrolysis of an acid anhydride can be regarded as the acylation of water; it is in many important respects analogous to the acylation of an amine. Thus it is known that structural factors which enhance the reactivity of the anhydride towards one of these reagents will also activate it for reaction with the other, though not to the same extent, the more reactive anhydrides apparently giving a higher value for the ratio k_1/k_2. Water is a very much less active reagent than the two amines (aniline and 2 : 4-dichloroaniline) used by us, and it therefore follows that, if primary ionisation is largely essential to the acylation of an amine, acylation of water molecules probably involves this step, particularly in view of the parallel trends of k_1, k_2 and k_1/k_2. The argument is not quite conclusive but, if accepted, leads to the following formulation of the hydrolysis mechanism :

$$CH_2Cl{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CH_2 \underset{K_{-1}'}{\overset{K_1'}{\rightleftharpoons}} CH_2{\cdot}CO^+ + CH_2Cl{\cdot}CO_2^-$$

$$CH_2{\cdot}CO^+ + H_2O \xrightarrow[K_2']{} CH_2{\cdot}CO_2H + H^+$$

and hence the rate equation :

$$V_{\text{Hydrolysis}} = \left\{K_{\text{H}} + K_{\text{H}}' + \frac{K_1'K_2'}{K_{-1}'[CH_2Cl{\cdot}CO_2^-] + K_2'}\right\}[\text{MA}] \quad . \quad . \quad . \quad . \quad \text{(xii)}$$

where K_{H} and K_{H}' are the rate coefficients for attack of water on the anhydride molecule in the two possible positions. (Since the reagent water is present in unchanging high concentration in the solvent, the constant K_2' is defined to include the function of the concentration of water on which the velocity depends.) This leads to the result that there should be an experimentally observable effect, according to which the velocity of hydrolysis is a linear function of the reciprocal of the concentration of chloroacetate ions.

(c) *Complicating Effects of Anions on Reactions of Acetic Chloroacetic Anhydride.*—Unfortunately, for several reasons, a straightforward test of this consequence of the ionisation mechanism is impossible : (1) The hydrolysis of symmetrical anhydrides is known to be base-catalysed; hydroxyl ions, anion bases, and tertiary amines have been shown to be effective and we have found pyridine also to be a catalyst for the hydrolysis of acetic chloroacetic anhydride. As a consequence the common-ion retardation by chloroacetate ions may be very largely masked by their opposite catalytic influence.

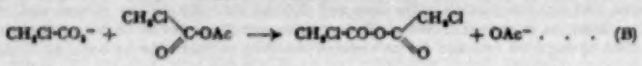
(2) Except at the very start of the reaction, the addition of a certain amount of acetate or chloroacetate ion to the reaction mixture does not produce a solution containing the same concentration of the added ion. Since chloroacetic and acetic acids are being formed throughout the reaction the concentrations of the ions at any moment are those appropriate to the mass law applied to the equilibrium :

$$CH_2{\cdot}CO_2^- + CH_2Cl{\cdot}CO_2H \rightleftharpoons CH_2Cl{\cdot}CO_2^- + CH_2{\cdot}CO_2H \quad . \quad . \quad . \quad . \quad \text{(A)}$$

with a secondary effect due to the direct ionisation of the acids.

(3) It is possible that the anion effect operates, not only through common-ion intervention in an ionisation mechanism, as discussed so far, but also through a bimolecular attack, and the experimental results of this paper relating to this are probably best explained by assuming this to be indeed an important factor. Since it is known that hydrolysis of an anhydride by hydroxyl ions proceeds at a rate several powers of ten greater than hydrolysis by water under conditions where a bimolecular mechanism is probable (Gold, *Trans. Faraday Soc.*, 1948, **44**,

506), it is not unlikely that the only slightly less nucleophilic acetate or chloroacetate ions can similarly effect a substitution more readily than water molecules. The reaction



leads to a symmetrical anhydride with a different tendency to hydrolyse compared with that of the mixed anhydride. It is analogous to:

A rapid reaction according to equation (B) is quite probable; Ruben, Allen, and Nahinsky (*J. Amer. Chem. Soc.*, **1942**, **64**, 3050) have observed that the radioactive exchange reaction:

$$CH_3\cdot\overset{*}{C}O\cdot ONa\ (solid) + (CH_3\cdot CO)_2O \longrightarrow CH_3\cdot\overset{*}{C}O\cdot O\cdot CO\cdot CH_3 + CH_3\cdot CO\cdot ONa$$

without added solvent is half-complete after only twenty minutes at room temperature, although sodium acetate is only slightly soluble in acetic anhydride.

(d) *Interpretation of Anion Effects.*—When these complications are taken into account, our experiments on acetate and chloroacetate ion addition may be interpreted as follows:

(1) Effect of acetate ions upon velocity of hydrolysis: During the early stages of the reaction, hydrolysis competes with the reaction:

$$CH_3\cdot CO_2^- + CH_2Cl\cdot CO\cdot O\cdot CO\cdot CH_3 \longrightarrow (CH_3\cdot CO)_2O + CH_2Cl\cdot CO_2^- \quad . \quad . \quad . \quad (C)$$

and [because of equilibrium (A)] to a smaller extent with the reaction (B). The first portion of the hydrolysis is therefore the rapid hydrolysis of a little chloroacetic anhydride and of mixed anhydride, catalysed by acetate and chloroacetate ions, followed by a slow portion, the length of which increases with the amount of acetate added, which corresponds mainly to hydrolysis of acetic anhydride (Fig. 2). The equilibrium position of reaction (C) is probably entirely on the right-hand side, since addition of chloroacetate ions to acetic anhydride did not produce a similar deviation from the first-order hydrolysis.

(2) Effect of acetate ions upon chloroacylation ratio: As the length of the slow portion of the hydrolysis increases, the proportion of chloroaceto-2:4-dichloroanilide in the acylation product decreases, for reactions in which acylation of 2:4-dichloroaniline and hydrolysis proceed at comparable speeds (Table VI). This is explained by the supposition that an increasingly larger portion of the acylation reaction is really acetylation by acetic anhydride. On the other hand, for the acylation of aniline, which proceeds at a much faster rate than either hydrolysis or the acetate substitution reaction, the chloroacylation ratio remains unchanged.

(3) Effect of chloroacetate ions upon velocity of hydrolysis: There is now considerable acceleration over most of the course of the reaction (Fig. 3) attributable to the formation and rapid hydrolysis of chloroacetic anhydride. The retardation at the end may be due to the slow hydrolysis of a small amount of acetic anhydride formed by the attack of acetate ions present, through attainment of the equilibrium (A).

(4) Effect of chloroacetate ions upon chloroacylation ratio: In agreement with the interpretation of (3) there is an increase in the chloroacylation ratio for 2:4-dichloroaniline with addition of chloroacetate ions, since the chloroacetic anhydride formed will naturally acylate to give exclusively the α-chloroacetanilide. As with acetate ions the chloroacylation ratio with aniline remains unchanged (Table VIII). It is only this last observation which seems to disprove without complication the existence of a common-ion effect in the reactions of acetic chloroacetic anhydride.

(5) Effect of acetate and chloroacetate ions upon the ratio hydrolysis/acylation: With acetic anhydride added basic catalysts hasten the hydrolysis relative to the acylation reaction. The effects observed with the mixed anhydrides (Table VI) do not, therefore, seem to call for a specific explanation, although the results do not, of course, relate to the hydrolysis of mixed anhydride alone, but to the mixed anhydride and an appreciable proportion of one or both of the symmetrical anhydrides.

On the whole, the effects of chloroacetate and acetate ions would seem to be too complex to permit the certain detection of common-ion and specific-ion intervention, and the interpretations of the effects given here are really independent of any assumed detailed mechanism.

Nevertheless, the failure to detect any phenomenon which can be attributed to a common-ion effect, and particularly its absence in the experiments on the chloroacylation ratio with aniline, suggest fairly strongly that an interpretation of the kinetics of the reactions by an ionic mechanism is not a probable one. To account for the absence of such effects in every instance it would be necessary to postulate details of mechanism both involved and at variance with those commonly accepted for ionisation mechanisms of organic reactions.

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299. *Quantitative Studies of the Reactivities of Mixed Carboxylic Anhydrides. Part III. The Hydrolysis and Some Acylation Reactions of a Series of Acetic Chloroaliphatic Acid Anhydrides.*

By A. R. EMERY and V. GOLD.

The mixed anhydrides of acetic acid with dichloroacetic, trichloroacetic, α- and β-chloropropionic, and γ-chlorobutyric acid have been prepared, and their hydrolysis velocities and the velocity of acylation of 2 : 4-dichloroaniline in acetone–water, as well as the product ratios for acylation of aromatic amines in different solvents, have been determined. The structural factors governing the reactions are discussed on the basis of the mechanisms proposed in the preceding papers. For acylation in benzene solution the activating inductive effect of chlorine substitution is opposed by a steric factor.

IN the preceding two papers a method of investigation into the nature and reaction mechanisms of mixed acid anhydrides was outlined, acetic chloroacetic anhydride being chosen as first example. The present paper deals with an extension of this work to other mixed anhydrides in which one of the parent acids is acetic acid and the other a carboxylic acid derived by substitution of one or more chlorine atoms in acetic, propionic, or *n*-butyric acid; some of the anhydrides are now reported for the first time. In this way a limited but systematic survey of the consequences of structural changes was carried out. The choice of the particular series of compounds investigated permitted their preparation by the keten method, and the employment of analytical methods which involved only minor modifications of those developed for acetic chloroacetic anhydride.

EXPERIMENTAL.

Most of the procedure and analytical methods for kinetic and product experiments are described in the preceding two papers.

Mixed anhydrides were prepared by the action of keten on the chloro-aliphatic acid in benzene solution and suspension, followed by vacuum-distillation at as low a temperature as practicable. Every specimen

TABLE I.*

Summary of results.

All data are for 25°. Results for k_1 and k_2 are for acetone–water (80 : 20 w/w) as solvent; for k_3 the amine used was 2 : 4-dichloroaniline.

Anhydride of acetic acid with	Chloroacylation ratio with aniline in benzene.	Chloroacylation ratio with aniline in acetone.	Chloroacylation ratio with aniline in acetone–water (80 : 20 w/w).	k_1/k_2.	$k_1 \times 10^4$.	$k_3 \times 10^5$ (overall).	$k_3 \times 10^5$ for chloroacylation portion.	$k_3 \times 10^5$ for acetylation portion.	Dissociation constant of chloroacid $\times 10^4$.†
Chloroacetic acid	0·1	1·6	0·69	0·78	576	74	21	53	155
Dichloroacetic acid	2·25	0·29	0·20	1·36	30,000	2,200	200	2,000	5,140
Trichloroacetic acid	0·08	0·07	—	—	Too rapid	—	—	—	120,000
α-Chloropropionic acid	0·94	0·45	0·27	0·22	205	65	8	57	147
β-Chloropropionic acid	0·29	0·25	0·20	0·16	13	7·0	0·8	7·1	8·6
γ-Chlorobutyric acid	0·36	0·37	0·41	—	0·2	—	—	—	3
Acetic acid	1	1	1	0·18	5·9	3·3	1·65	1·65	1·8

* Symbols are defined in the preceding paper.

† Since thermodynamic dissociation constants have not been measured in all cases, classical dissociation constants are quoted throughout.

used was analysed for (i) chlorine content, (ii) the amount of acid produced on complete hydrolysis of a weighed sample, (iii) the amount of acid produced after reaction with excess of dry aniline in the cold (see *J.*, 1950, 1443), and usually all analyses were within 1% of the theoretical values. The purity was also checked by (*a*) constancy of refractive index during distillation (within ±0·0005), and (*b*) strict first-order character of all hydrolysis velocities. In all reaction-velocity measurements it was verified that the arresting solution employed (aniline in either the solvent used in the hydrolysis or in acetone) was satisfactory. For determination of reaction products it was verified that the chloroacyl derivative was stable under the conditions of the extractions.

Most of the results are summarised in Table I; some additional data are given below under the appropriate headings for each anhydride.

(i) *Acetic dichloroacetic anhydride* (b. p. 34—37°/~0·01 mm., n_D^{15} 1·4498). The sample did not crystallise on cooling to −80°. See Tables II and III.

TABLE II.

Product composition for the acylation of two primary aromatic amines with acetic dichloroacetic anhydride in different solvents. $[MA]_0$ ~0·05M.† $[Amine]_0$ ~1M.

Experiment.	Solvent.	Temp.	Chloroacylation ratio with aniline.	Chloroacylation ratio with 2 : 4-dichloroaniline.
1 (*a*), (*b*)	Benzene	25°	2·25	2·35
2	Benzene–acetone (80 : 20 w/w)	18	1·45	—
3	Benzene–acetone (50 : 50 w/w)	18	0·67	—
4	Acetone	18	0·29	—
5 (*a*), (*b*)	Acetone–water (80 : 20 w/w)	25	0·20	0·12 •
6	Acetone–water (50 : 50 w/w)	18	0·21	—

• In this experiment 73·6% of the total reaction is hydrolysis, giving k_1/k_2 = 1·36 moles l.$^{-1}$.
† MA = mixed anhydride.

TABLE III.

Velocity of hydrolysis of acetic dichloroacetic anhydride in acetone–water (80 : 20 w/w). $[MA]_0$ ~0·1M.

Temp.	$k_1 \times 10^3$ (secs.$^{-1}$).	*E*.
0·3°	6·5	9·8 kcals.
25·1	30	

(ii) *Acetic trichloroacetic anhydride* (b. p. 30—34°/~0·05 mm., f. p. −5° approx.). Reaction with aniline in acetone–water (80 : 20 w/w) led to 13% hydrolysis and 87% acylation; acylation is 100% in dry solvents. Hydrolysis is too rapid for measurement in 80% acetone–water. Rate of hydrolysis in undried AnalaR acetone (containing 0·5—1% of water) at 25°, k_1 = 4·2 × 10^{-4} sec.$^{-1}$; after addition of 1·83% of water (w/w), k_1 = 3·2 × 10^{-3} sec.$^{-1}$.

(iii) *Acetic α-chloropropionic anhydride* (b. p. 35—36°/~0·005 mm., n_D^{15} 1·4295). See Table IV.

TABLE IV.

Competitive acylation–hydrolysis experiments with acetic α-chloropropionic anhydride and 2 : 4*-dichloroaniline in acetone–water* (80 : 20 w/w). Temp., 25·1°. $[MA]_0$ ~0·06M.

$[Amine]_0$.	Hydrolysis, %.	k_1/k_2.	$k_2 \times 10^4$.	Chloroacylation ratio.
0·125	72·5	0·31	6·6	—
0·250	60·1	0·35	5·8	—
0·533	36·1	0·29	7·1	0·15

(iv) *Acetic β-chloropropionic anhydride* (b. p. 41—43°/~0·01 mm., n_D^{15} 1·4302). The influence of acetate and β-chloropropionate ions on the various reactions is complicated through side reactions. Chloroacylation ratio with 2 : 4-dichloroaniline in acetone–water (80 : 20 w/w) = 0·12.

(v) *Acetic γ-chlorobutyric anhydride* (b. p. 51—54°/~0·005 mm., n_D^{25} 1·4421).

DISCUSSION.

(a) *The Chloroacylation Ratios in Benzene.*—In our discussion of the reaction between an aromatic amine and acetic chloroacetic anhydride in benzene solution (*J.*, 1950, 1443) it was argued that the predominant reaction in the attack of molecular anhydride on excess of amine would be the one introducing the acyl group containing the carbonyl-carbon atom which was poorer in electrons, *e.g.*, in the case of acetic chloroacetic anhydride, chloroacetylation would take place to a larger extent than acetylation. Hence, if a series of mixed acetic anhydrides R·CO·O·CO·CH_3 were investigated in which the electron attraction of the group R was altered systematically without changing any other structural factors, one should obtain a whole gamut of chloroacylation ratios according to the sequence of electronic-attraction powers.

The results for the mixed anhydrides of acetic acid with the three chloroacetic acids show that a theory which assumes such a naïve model to be applicable to these compounds is too simple, and its failure seems to be due chiefly to the neglect of a steric factor. Alternatively, it would be possible to explain the experimental sequence of chloroacylation ratios by postulating the occurrence of an ionisation mechanism in benzene, but it would be difficult to uphold such a contention on other grounds.

It is well known that in the bimolecular nucleophilic replacement reactions of the series of alkyl halides

$$CH_3{\cdot}CH_2{\cdot}X \qquad MeCH_2{\cdot}CH_2{\cdot}X \qquad Me_2CH{\cdot}CH_2{\cdot}X \qquad Me_3C{\cdot}CH_2{\cdot}X$$

the reaction velocity decreases throughout the series. This decrease has been attributed to the combined operation of an electronic and a steric effect, the latter being of more decisive importance for the later members of the series (Hughes, *Trans. Faraday Soc.*, 1941, **37**, 620; Dostrovsky, Hughes, and Ingold, *J.*, 1946, 173; cf. A. G. Evans, *Trans. Faraday Soc.*, 1946, **42**, 719). In the case of our series

$$\overset{a}{CH_3}{\cdot}CO{\cdot}OAc \qquad \overset{a}{ClCH_2}{\cdot}CO{\cdot}OAc \qquad \overset{a}{Cl_2CH}{\cdot}CO{\cdot}OAc \qquad \overset{a}{Cl_3C}{\cdot}CO{\cdot}OAc$$

the steric effect of successive chlorine substitutions on a bimolecular nucleophilic replacement reaction at *a* would be expected to exert a retarding influence analogous to the effect of methyl groups in the above series of β-methylated ethyl halides, the two structures being very similar. On the other hand, the electronic effect will be in the opposite direction. Thus, for the β-methylated ethyl halides steric hindrance and electron repulsion of methyl groups towards the seat of substitution tend to reinforce each other in reducing the reaction rate; however, in the chloroacetyl acetates the electron withdrawal by the chlorine atoms favours substitution, whereas the steric hindrance effect will tend to retard it. By analogy with the results of Dostrovsky, Hughes, and Ingold (*loc. cit.*) we expect the electronic effect to be most important near the beginning of the series and the steric effect most important for the highly substituted members. As a consequence the highest reactivity for nucleophilic substitution at *a* may be found in a member somewhere along the series and not necessarily at one of its ends. The case of the chloroacetyl acetates is, however, different from that of the β-methylated ethyl halides, in that the latter compounds cannot undergo any alternative substitution reaction at a carbon atom other than that at which the replacement reaction is sterically hindered, whereas the mixed anhydrides have the alternative centre of substitution *b*:

$$\overset{a}{Cl_3C}{\cdot}CO{\cdot}O{\cdot}CO{\cdot}\overset{b}{CH_3}$$

(*i.e.*, replacement of the trichloroacetate group in acetyl trichloroacetate instead of the replacement of the acetate group in trichloroacetyl acetate), and in the competition of the two halves of the molecule for the nucleophilic reagent steric hindrance will favour position *b* relative to *a*. The combined operation of the electronic and a steric influence in opposition to each other will therefore explain the observed sequence of chloroacylation ratios:

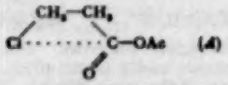
$Cl{\cdot}CH_2{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CH_3$	$Cl_2CH{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CH_3$	$CH_3{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CH_3$	$Cl_3C{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CH_3$
0·1	2·3	1	0·08

In comparing various acetic chloro-aliphatic anhydrides by means of the chloroacylation ratios in benzene it must be appreciated that the "reference half" of the molecule (*i.e.*, the acetyl group) is not really constant throughout the series, since the electronic effect in the other half will be transmitted to it, though somewhat weakened.

The chloroacylation ratio of acetic α-chloropropionic anhydride is readily intelligible on this basis. Steric hindrance by the two groups, methyl and chlorine, may be of the same order of magnitude as that of the two chlorine atoms in acetic dichloroacetic anhydride, but the electronic effect of the methyl group tends to hinder substitution in opposition to the effect of the chlorine atom. The ratio is therefore appreciably lower than for acetic dichloroacetic anhydride.

On the other hand, the cases of acetic β-chloropropionic anhydride and acetic γ-chlorobutyric anhydride call for special comment. In both these anhydrides the chlorine substitution might be thought to be sufficiently far removed from the centre of the replacement reaction not to cause any compressional increment in the energy of activation of the reaction, so that the chloroacylation ratios should follow the sequence dictated by the magnitude of the positive charge on the carbonyl-carbon atom of the chloroacyl group; an indication of this sequence

should be given by the acid dissociation constant of the parent chloro-aliphatic acid. However, on this basis the chloroacylation ratios are in the wrong order, the discrepancy being experimentally significant. It is of particular importance that both ratios are less than unity, a fact which is unintelligible if there is no steric hindrance. It is suggested that the lowered reactivity of the chloroacyl group is due to the internal screening of the reaction centre through electrostatic interaction between the chlorine atom and the positive end of the carbonyl group dipole.



(*A*)

It may well be that the mixed anhydrides for which this effect makes the most significant contribution to the free energy of activation of the reaction are the acetic β-chloro-aliphatic anhydrides, since the " locked " configuration (*A*) will involve a greater loss of entropy in the case of longer chains. It is impossible to specify whether the retardation caused is only due to reduction of the effective positive charge on the carbon atom through induction across space (the old " direct " or " field effect "), or whether it should be regarded as brought about by the blocking of the direction of approach of the nucleophilic reagent by the chlorine atom. Any similar interaction between the chlorine atom and the carbonyl-carbon atom of the more remote acetyl group will presumably be much smaller, but it is not possible to say how important this is. Neither can we assess whether a certain portion of the " steric hindrance " in acetic α-chloro-aliphatic anhydrides should be regarded as a field effect acting in addition to the compression-energy effect discussed by Dostrovsky, Hughes, and Ingold (*loc. cit.*).

(b) *Chloroacylation Ratios in Acetone–Water.*—As was mentioned in Part I, there is a strong dependence of the chloroacylation ratio on the nature of the solvent and we have considered two interpretations of this effect. One of these which assumes a change of reaction mechanism is, however, rendered improbable by the kinetic evidence of Part II. The second explanation, which follows, is based on steric solvent effects which are thought to arise in a similar way to the steric factor which appears in the structural influence on chloroacylation ratios in benzene solution and which was discussed in the preceding section.

We envisage the geometry of the transition states for the two acylation reactions of aniline as follows :

The two transition states are very similar and changes in their electrostatic solvation—which will be important to the stability of both structures—are unlikely to bring about a reversal of their relative stabilities. A change in solvent, insofar as its effect on the transition state is that of a solvating dielectric, should therefore make *both* transition states either more or less stable, although probably not to the same extent. Thus it will modify the value of the chloroacylation ratio but it is unlikely to change it from >1 to <1.

The transition state for chloroacetylation involves the possibility of steric repulsion (or interpenetration) between the chlorine atom and atoms in the amine molecule and acetate group. This repulsion would be greater than any analogous effect in the transition state for acetylation where the smaller hydrogen atoms of the methyl group would be involved. Taking account of the relevant distances of the atoms concerned, it seems probable that there will not be much steric strain in either transition state, and it is only when several large atoms are attached to the carbon atoms adjacent to the seat of substitution that the effect will assume any great importance, as discussed above.

However, it is now suggested that steric hindrance may also make itself felt if solute–solvent attraction increases the size of the amine molecule. Such interaction would presumably be unimportant for solutions in benzene. In the presence of water, on the other hand, we may get solvation of the amino-group through hydrogen-bonding. This seems quite plausible when we consider the enhanced solubility, in water, of an organic molecule after the introduction of an amino-group. The amine is also likely to form a hydrogen-bonded complex with acetone, since intramolecular hydrogen-bonding between amino- and carbonyl groups is well established.

With a fair excess of acetone most of the amine may, in fact, be associated with acetone. If solvent molecules become attached to the amine in this manner, we may now find that the transition state is sterically strained, *i.e.*, that there is interpenetration of the solvated-amine part and the substituents on the α-carbon atom of the anhydride portion :

The solvent attachment would, therefore, favour reaction at the less heavily substituted half of the anhydride. This effect may be accentuated by the higher degree of solvent orientation around the more polar, substituted half of the anhydride molecule. The discrimination may become even more marked if solvation of the amine causes a higher electron density at the nitrogen atom, as would be expected if the solvation is due to hydrogen-bonding from one of the hydrogen atoms of the amino-group. In that case the acylation of the solvated amine will be more rapid than that of the unsolvated molecule, provided that steric hindrance does not nullify this increased reactivity.

It follows from such an explanation that the operation of this solvent effect, which favours acetylation at the expense of chloroacylation, would depend on the power of the solvent to attach itself and on the geometry of the complex formed, and no direct significance would attach to the apparent functional dependence of the chloroacylation ratio on the dielectric constants of the particular solvent mixtures employed. In the absence of any tangible evidence of the structure of these complexes we shall not attempt to elaborate this hypothesis by further speculation. If this, or a similar, interpretation is correct, it would mean that the reversal of the chloroacylation ratio is merely due to a minor specific medium effect which assumes a decisive rôle in the case of its differentiating operation towards two reactions which are very nearly equally important.

Experimental results similar to those found for acetic chloroacetic anhydride have been observed for other acetic halogeno-aliphatic acid anhydrides. Again the chloroacylation ratio appears to decrease with increasing polarity of the solvent, but the effect is absent or not marked for those anhydrides which give a low chloroacylation ratio even in benzene. However, this conclusion must be accepted with some reserve since small chloroacylation ratios are liable to larger percentage errors.

(c) *Velocities of Acylation and Hydrolysis.*—It was pointed out in the preceding two papers that both these velocities are complicated, since they express the sum of different reactions. They do not, therefore, correspond to comparable processes in all cases. However, one would still expect an orderly sequence in these velocities, following the electronic effect of the varying group, provided that the substances are sufficiently closely related structurally. Indeed, we find a parallelism between the rates of hydrolysis and the acid dissociation constants of the parent chloro-aliphatic acids.

We have interpreted the fall of the chloroacylation ratio along the series of acetic α-chloroacetic anhydrides in benzene as due to the intervention of a steric factor. Nevertheless, our data show that the velocity of chloroacylation in acetone–water—which, on either of our interpretations of the solvent effect, has also been attributed to the same bimolecular mechanism—still rises throughout the series, which may appear to contradict the idea of steric hindrance. This apparent contradiction does not arise if the steric explanation of the low chloroacylation ratios in heavily substituted anhydrides is put, more correctly, in a somewhat modified form. When α-chlorine atoms are introduced into one half of the anhydride molecule there is electronic activation of both carbonyl positions. However, since the nearer potential reaction centre is sterically hindered by this same substitution, the activation is *more* noticeable at the more remote carbonyl position, in spite of the fact that the electronic effect is actually weaker there. This is illustrated by a comparison of the eighth and the ninth column of Table I. Both halves of the molecule are seen to be more reactive than in the unhindered anhydride but the increase in reactivity is greater in the unsubstituted half.

(d) *Values of the Ratio* k_1/k_2.—It may be noted that this ratio appears to increase fairly systematically with the reactivity of the anhydride (*i.e.*, its rate of hydrolysis or acylation), both for mixed and symmetrical anhydrides (Table I, and Part II, Table III). This observation

probably constitutes the strongest single item of evidence against a mechanism of acylation by acetic chloro-aliphatic anhydrides through intermediate acylium ions. In an ionic mechanism, the reactions of the mixed anhydrides studied by us would in every instance be the result of attack by the same species, *viz.*, $CH_3{\cdot}CO^+$. The ratio of the reactivities of this species for amine and for water should then be independent of the nature of the other half of the molecule which, as anion, would take no direct part in the reactions. For ionic mechanisms of the reactions of these mixed anhydrides, k_1/k_2 should, therefore, be constant.

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300. *Lead Alunite.*

By HENRY BASSETT.

A preparation of lead alunite has been obtained which contains 44% of $Pb(Al_3(OH)_6(H_2O)_2][SO_4]_2$ mixed with $H_3O[Al_3(OH)_6H_2O][SO_4]_2$ and a little $H_3O[Al_3(OH)_6(H_2O)_2][Al(OH)_4]_2$. This gives valuable support to the view that in the alunite lattice one-third of the aluminium positions can be vacant.

ALUNITE, $K[Al_3(OH)_6][SO_4]_2$ is the first and best-known member of a group of minerals in which isomorphous replacement of a very varied character can occur (Hendricks, *Amer. Min.*, **1937**, **22**, 772). Such replacement can be of the simple type (K^+ by NH_4^+, Na^+, Rb^+; Al^{3+} by Fe^{3+}) or of a compensatory nature. The latter type of replacement is found in some minerals of the alunite group which contain lead, strontium, or barium in place of alkali metal. The extra positive charge of the bivalent metal is balanced by replacement of some of the SO_4'' by PO_4''' or AsO_4'''. Hinsdalite, $Pb[Al_3(OH)_6][SO_4][PO_4]$ is of this nature. Plumbojarosite is considered by Hendricks to be $Pb[Fe_3(OH)_6]_2[SO_4]_4$ with one of the potassium positions vacant.

The $Al_3(OH)_6$ or $Fe_3(OH)_6$ is part of an endless band of AlO_6 or FeO_6 octahedra in which each Al or Fe ion is surrounded by four hydroxyl ions and by two oxygen atoms of SO_4 ions. The latter are in *trans*-positions in the octahedra which are joined by their edges, two hydroxyl ions being shared by two octahedra.

Hendricks showed that one of the six hydroxyl ions could be replaced by a water molecule but as the $[Al_3(OH)_6H_2O]$ group carried four positive charges no potassium ion is required to balance the charges on the two SO_4 ions. The place of the potassium in the crystal lattice is therefore taken by another water molecule.

According to the results of Bassett and Goodwin (*J.*, **1949**, 2254) more than one of the six hydroxyl ions can be replaced by water molecules if one of the three octahedral postions contains no Al^{3+} or Fe^{3+}. There originate in this way compounds such as $K[Al_3(OH)_6(H_2O)_2][SO_4]_2$, $H_3O[Al_3(OH)_6(H_2O)_4][SO_4]_2$, and $H_3O[Al_3(OH)_6(H_2O)_2][Al(OH)_4]_2$. Most members of the alunite group containing Pb^{2+}, Sr^{2+}, or Ba^{2+} contain phosphate (or arsenate) in addition to sulphate, but it would seem from the above that a compound $Pb[Al_3(OH)_6(H_2O)_2][SO_4]_2$ should be obtainable and be a true alunite. The existence of this compound would give strong additional support to the view that vacant octahedral positions can occur in the alunite lattice.

A preparation has been obtained which according to the analysis contains about 44% of alunite with the above formula, the remainder consisting chiefly of $H_3O[Al_3(OH)_6H_2O][SO_4]_2$. It gives an excellent *X*-ray diagram of alunite and is much less soluble than is lead sulphate, just as the normal alunites are much less soluble than the alkali-metal sulphates.

It is possible that some modification of the preparative procedure might give a product with a composition nearer to that of pure $Pb[Al_3(OH)_6(H_2O)_2][SO_4]_2$. This is not at all certain, however, since isomorphous replacement by $H_3O[Al_3(OH)_6H_2O][SO_4]_2$ and $H_3O[Al_3(OH)_6(H_2O)_2][Al(OH)_4]_2$ occurs so readily. The author is not able at present to carry out further experiments to settle this point.

Attempts to prepare calcium, strontium, and barium alunites in a similar way to the lead compound gave products which are probably mixtures of the desired alunites and the corresponding sulphates. It has not been possible to attempt to separate these.

Similar experiments with basic aluminium sulphate solutions to which manganese, nickel or cadmium salts had been added gave relatively small amounts of precipitates consisting of the glassy solid of Two-liquid System I of the system Al_2O_3–SO_3–H_2O (Bassett and Goodwin,

loc. cit., p. 2257). Only the precipitate from the cadmium experiment was actually analysed. It was easily soluble in dilute acid and contained no cadmium. The ionic radii of these three metals are not greatly different from those of the alkali and alkaline-earth metals and for that reason it seemed worth while to see whether they could yield alunites. If these existed they would probably be soluble with difficulty in acids.

Experimental.

A basic aluminium sulphate solution was prepared from N-sulphuric acid (100 c.c.), aluminium (1·232 g.), and a drop of mercury. The finely divided mercury was removed by filtration and a solution of lead nitrate (3·178 g.) in water (20 c.c.) slowly added with vigorous stirring to the boiling mixture. This is the amount of lead nitrate which would have been needed to precipitate all the $Al_4(OH)_6SO_4$ as alunite if the basic solution was considered to contain only $Al_2(OH)_4SO_4$ and $Al_2(SO_4)_3$.

The mixture was heated on a hot plate to about 75° for 4 weeks with occasional stirring and replacement of water lost by evaporation. The precipitate was then filtered off on a hardened filter paper on a Buchner funnel and washed with cold water (75 c.c.), followed by rectified spirit (25 c.c.), and weighed 6·02 g. after being dried in the air.

Under the microscope the solid was seen to consist apparently of a mixture of very minute prisms of lead sulphate and minute square crystals of alunite. Its *X*-ray diagram showed the lines of these two compounds. Treatment at room temperature with 2N-hydrochloric acid removed all the free lead sulphate. Extraction of 1 g. of the solid with 25 c.c. of the 2N-acid for 3½ hours removed lead sulphate representing 26·6% of the original solid, and a further 25 c.c. during 24 hours removed a further quantity equivalent to only 1·9% of the original solid. The extracts contained only a trace of alumina. The residual material appeared to consist of very minute square crystals with a high double refraction. No prisms of lead sulphate could be detected. It gave an excellent alunite *X*-ray diagram which showed none of the lead sulphate lines. It was quite free from chloride, which showed that there had been no replacement of hydroxyl by chlorine during the treatment with hydrochloric acid.

Method of Analysis.—Owing to its insolubility in hydrochloric acid the lead alunite (air-dried) was analysed as follows: It was boiled for 15 minutes with aqueous sodium carbonate (1·5 g. in 15 c.c. of water for 0·2 g. of lead alunite), the mixture being well stirred and crushed several times with a glass rod. After the 15 minutes' boiling the mixture was diluted with boiling water (65 c.c.), allowed to cool, and set aside for 4 hours before filtration, and washing, with decantation, with about 100 c.c of water. Solid on the paper was rinsed into the beaker in which most of the solid still remained and 10 c.c. of hot 2N-hydrochloric acid were poured through the filter into the beaker. This was sufficient to dissolve the precipitate completely, showing that attack of the alunite had been complete.

The alkaline filtrate from the lead carbonate was acidified with 2N-hydrochloric acid and a further 15 c.c. were added to the 200 c.c. of solution before precipitation of the sulphate. After removal of excess of barium from the barium sulphate filtrate the alumina in solution was precipitated with ammonia and weighed as Al_2O_3 after ignition at 1000—1100°. The precise nature of the lead compound obtained by the digestion with sodium carbonate is uncertain. It contains both lead and sodium carbonate but also more than half of the alumina originally present in the lead alunite. The lead in the acid solution was converted into sulphate by evaporation with sulphuric acid, and the lead sulphate filtered off and weighed on a sintered-glass Gooch crucible after drying at 100°. The alumina also present was precipitated with ammonia in the filtrate from the lead sulphate and weighed as Al_2O_3. The composition found by analysis was: PbO, 17·7; Al_2O_3, 29·9; SO_3, 34·7; H_2O (by difference), 17·7%. This composition can be expressed conveniently and very closely in terms of the mixture of alunites:

$$Pb[Al_3(OH)_6(H_2O)_3][SO_4]_2,\ 44{\cdot}1;$$
$$H_3O[Al_3(OH)_6H_2O][SO_4]_2,\ 54{\cdot}35;$$
$$H_3O[Al_3(OH)_6(H_2O)_3][Al(OH)_4]_2,\ 1{\cdot}2\%.$$

This leaves 0·35% of water unaccounted for, which may well have been adsorbed on the very fine solid. The solid is to be regarded as an essentially homogeneous solid solution with random distribution of the various ions or groups which can replace one another.

The *X*-ray examination of the lead alunite was made by Dr. G. B. Greenough, to whom I express my thanks.

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301. *Oxidation of Aldehydes in the Gaseous Phase. Part III. The Inhibition of the Oxidation of Acetaldehyde by Nitrogen Peroxide (Dioxide).*

By C. A. McDowell and J. H. Thomas.

The inhibition, by nitrogen peroxide (dioxide), of the low-temperature gas-phase oxidation of acetaldehyde has been studied in detail and it is shown that this compound acts as a strong inhibitor. From a theoretical treatment of this type of inhibition it is shown that the initiation process is a bimolecular reaction between acetaldehyde and oxygen. To account for the experimentally determined activation energy of this reaction it is suggested that the initiation reaction is $CH_3{\cdot}CHO + O_2 = CH_3{\cdot}CO + HO_2$.

The simple theoretical treatment outlined leads to an expression for the rate of initiation, r_i, which with the experimental results recorded in this paper has a value of $7{\cdot}2 \times 10^{-6}$ mole litre^{-1} sec.$^{-1}$ at 141°. The chain length of the oxidation is shown to be very short.

In Part I (*J.*, 1949, 2208) it was shown that the gas-phase oxidation of acetaldehyde is strongly inhibited by small quantities of nitrogen peroxide, and that the inhibition is characterised by a long induction period during which there is practically no change in pressure. At the end of this induction period the pressure falls and the rate of decrease soon becomes approximately the same as that for the uninhibited reaction. The inhibition of a reaction by small quantities of foreign compounds shows that it is characterised by having a chain mechanism; and by a careful study of inhibited reactions it is often possible to derive important information concerning the underlying chain processes (Bäckström, *J. Amer. Chem. Soc.*, 1927, **49**, 1469; *Meddel. K. Veten. Akad. Nobelinst.*, 1927, **6**, Nos. 15, 16; Alyea and Bäckström, *J. Amer. Chem. Soc.*, 1929, **51**, 90; Hinshelwood, "Kinetics of Chemical Change," Oxford, 1940; Semenoff, "Kinetics of Chain Reactions," Oxford, 1935).

The rate of an inhibited chain reaction can be written as

$$R = r_i r_p/(r_t + k_I I) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where r_i = rate of initiation of chains, r_p = rate of propagation of chains, r_t = rate of termination of chains by normal process, and $k_I I$ = rate of termination of chains by inhibitor of concentration I.

From equation (1) it is seen that a linear relation exists between the reciprocal of the rate of an inhibited reaction and the concentration of the inhibitor. Pease (*J. Amer. Chem. Soc.*, 1933, **55**, 2753) showed that ethyl alcohol inhibited the gas-phase oxidation of acetaldehyde and found that the inhibited reaction obeyed this linear relation.

From equation (1) it is also possible to obtain a simple relation between the induction period and the concentration of inhibitor in the case of a strongly inhibited reaction. The length of the induction period τ will be inversely proportional to the rate of reaction R; then from the above equation we have

$$\tau = K/R = Kr_t/r_i r_p + Kk_I I/r_i r_p \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where K is a constant for the particular reaction. Thus a plot of τ against I should be linear.

In Fig. 1 we have plotted the induction period τ against the initial concentration of the nitrogen peroxide for several temperatures, and it is seen that the linear relationship is obeyed, thus proving beyond all reasonable doubt that the gas-phase oxidation of acetaldehyde is a chain reaction. At the end of the reaction all the brown colour of the nitrogen peroxide initially present has disappeared, showing that the inhibitor, or some compound derived from it, does in fact react with the radicals produced in the chain reaction.

Since in the uninhibited reaction there is practically no induction period (see Part I) and the pressure decreases from the start of the reaction owing to the formation of peracetic acid, the only reasonable interpretation of the induction period produced by nitrogen peroxide is that it is preventing the formation of peracetic acid and so it, or some compound derived from it, must react with the chain initiator.

One can make use of this linear relation between the induction period and the initial concentration of the inhibitor to investigate the nature of the initiation reaction in the oxidation. From equation (1), the fraction of chains terminated by the inhibitor will be $k_I I/(r_t + k_I I)$, so if one molecule of inhibitor is consumed for each chain terminated, the rate of disappearance of the inhibitor will be

$$-\mathrm{d}I/\mathrm{d}t = r_i k_I I/(r_t + k_I I) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

If the compound under investigation is a strong inhibitor, as is nitrogen peroxide in this system, then $k_3 I \gg r_i$, and equation (3) becomes

$$-dI/dt \approx r_i \quad \ldots \quad (4)$$

i.e., the rate of disappearance, or consumption, of inhibitor equals the rate of the initiation of chains.

Integration of equation (4) gives

$$I_0 - I_t = r_i t \quad \ldots \quad (5)$$

where I_0 and I_t are, respectively, the concentrations of inhibitor initially and at time t. If at the end of the induction period, *i.e.*, when $t = \tau$, all, or most, of the inhibitor is consumed, $I_0 \gg I_t$, so $I_0 - I_t \approx I_0$ and we can write

$$I_0/\tau \approx r_i \quad \ldots \quad (6)$$

Other workers have previously derived equation (6) in a similar manner and have shown it to be obeyed approximately in the cases of the inhibition of the liquid-phase oxidation of

FIG. 1.

Variation of induction period with concentration of inhibitor.

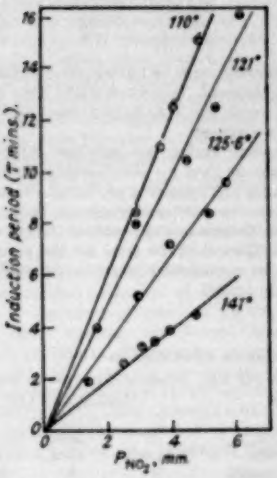
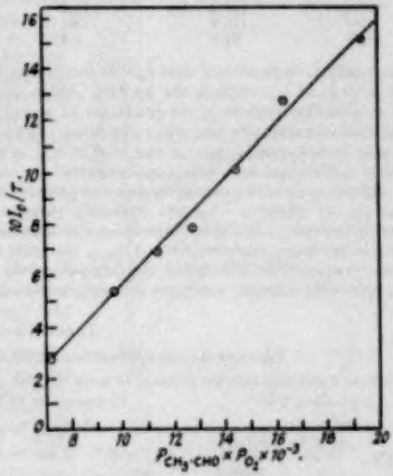


FIG. 2.

Variation of rate of initiation with concentration of reactants.



tetralin (George, Rideal, and Robertson, *Proc. Roy. Soc.*, 1946, *A*, **185**, 288) and of the polymerisation of styrene and other monomers by quinones (Foord, *J.*, 1940, 48; Goldfinger, Skeist, and Mark, *J. Physical Chem.*, 1943, **47**, 578; Melville and Watson, *Trans. Faraday Soc.*, 1948, **44**, 886).

Bodenstein (*Sitzungsber. Preuss. Akad. Wiss., Phys.-Math. Kl.*, 1931, III, 1) gave the following reactions for the initiation of the oxidation of acetaldehyde:

$$A = A^* \quad \ldots \quad (A)$$

$$A^* + O_2 = P^* \quad \ldots \quad (B)$$

In Part I it was suggested that a more likely initiation process is the simple bimolecular reaction

$$CH_3\cdot CHO + O_2 = CH_3\cdot CO + HO_2 \quad \ldots \quad (C)$$

followed by the reaction

$$CH_3\cdot CO + O_2 = CH_3\cdot CO_3 \quad \ldots \quad (D)$$

The initiation step (C) was also proposed earlier by Keyer and Neumann (*Acta Physicochim., U.R.S.S.*, 1941, **14**, 451).

Equation (6) can be used in the following way to decide between the unimolecular process

given by Bodenstein and a bimolecular initiation process such as that suggested by us. If we determine I_0/τ for a series of mixtures with different aldehyde/oxygen ratios, for the former case we should have a linear relation between I_0/τ and the concentration of the aldehyde, whereas if the bimolecular process is correct, we should only obtain a linear relation between I_0/τ and the product of the concentrations of acetaldehyde and oxygen.

Table I shows the effect on the induction period of varying the aldehyde/oxygen ratio whilst keeping the amount of inhibitor approximately constant. Col. 3 gives the product [Aldehyde][Oxygen], and col. 6 the corresponding value of I_0/τ.

TABLE I.

Effect on the induction period of varying the aldehyde/oxygen ratio in mixtures of acetaldehyde, oxygen, and nitrogen peroxide.

Temperature 125·7°.

$[CH_3CHO]$, mm.	$[O_2]$, mm.	$[CH_3CHO][O_2] \times 10^{-4}$.	$[NO_2]$, mm.	τ, mins.	I_0/τ.
104·1	180·8	19·4	4·9	2·25	1·52
150·1	109·1	16·4	5·4	4·2	1·28
103·2	141·1	14·5	4·9	4·8	1·02
113·5	112·9	12·8	5·2	6·6	0·79
103·4	110·5	11·4	5·2	8·25	0·605
87·0	111·7	9·7	5·4	10·0	0·54
104·1	69·0	7·2	4·9	17·6	0·282

These results show clearly that I_0/τ does not vary linearly with the aldehyde concentration. A plot (Fig. 2) of I_0/τ against the product [Aldehyde][Oxygen], yields a straight line, showing that the initiation process in the oxidation of acetaldehyde is a bimolecular reaction between oxygen and acetaldehyde and also confirming the above theory.

It was stated earlier that at the end of the induction period the pressure dropped and continued to decrease at a rate approximately the same as that for the uninhibited reaction. Closer examination of the rate of decrease of pressure after the induction period as a function of the amount of nitrogen peroxide originally present in the mixture brings to light certain interesting features. In Table II are given the induction periods and the rates of the subsequent decrease in pressure, represented as $1/t_{10-50}$ (*i.e.*, the reciprocal of the time for the pressure to fall from 10 mm. to 50 mm. below the original value), for a particular mixture of acetaldehyde and oxygen with different amounts of nitrogen peroxide added.

TABLE II.

Effect of nitrogen peroxide concentration on main reaction.

Throughout these experiments pressure of acetaldehyde = 103 mm., pressure of oxygen = 107 mm.

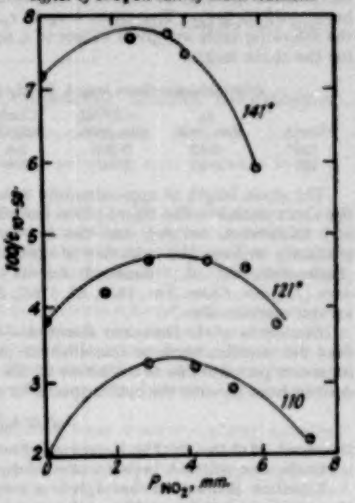
Temperature 110°.			Temperature 121°.			Temperature 141°.		
NO_2, mm.	Induction period, mins.	$1/t_{10-50}$, min.$^{-1}$.	NO_2, mm.	Induction period, mins.	$1/t_{10-50}$, min.$^{-1}$.	NO_2, mm.	Induction period, mins.	$1/t_{10-50}$, min.$^{-1}$.
0	0	0·0202	0	0	0·0383	0	0	0·0720
2·9	8·5	0·0325	1·7	4·0	0·0422	2·5	2·6	0·0770
3·7	11·0	0·0328	2·9	8·0	0·0465	3·3	3·1	0·0861
4·1	12·5	0·0322	4·5	10·5	0·0467	3·5	3·5	0·0861
5·0	15·1	0·0288	5·4	12·5	0·0455	4·0	3·9	0·0747
7·3	21·8	0·0218	6·2	16·1	0·0327	4·8	4·5	—
						5·9	—	0·0393

In Fig. 3 we have plotted $1/t_{10-50}$ against the pressure of nitrogen peroxide added. The curves show that nitrogen peroxide, or a product derived from it, has a catalytic effect on the reaction following the induction period up to about 3 mm., or 1·3% of nitrogen peroxide added, after which the rate begins to decrease. This influence of nitrogen peroxide on the main acetaldehyde–oxygen reaction between 110° and 140° is very similar to that observed by Kane (*Proc. Roy. Soc.*, 1939, *A*, **171**, 251) on the acetaldehyde cool flame. He found that the addition of small quantities of nitrogen peroxide had a promoting effect on the ignition of acetaldehyde–oxygen mixtures at 260°, *i.e.*, the minimum ignition pressure was considerably lowered. Larger amounts of nitrogen peroxide (greater than 3%) caused the ignition pressure to increase again. The time lag before ignition continued to increase with the amount of inhibition added. This is exactly parallel to our observations in the 110—141° temperature range.

The catalytic effect of nitrogen peroxide on the main oxidation reaction is presumably due to small amounts of this compound which are left at the end of the induction period. This influence of the residual nitrogen peroxide on the oxidation is probably very similar to its sensitization of the hydrogen–oxygen reaction (Dixon, *Trans. Inst. Min. Eng.*, 1930—1931, **80**, 21; Gibson and Hinshelwood, *Trans. Faraday Soc.*, 1928, **27**, 559; Thompson and Hinshelwood, *Proc. Roy. Soc.*, 1929, *A*, **124**, 219; Norrish and Griffith, *ibid.*, 1933, *A*, **139**, 147; Foord and Norrish, *ibid.*, 1935, *A*, **152**, 196; 1936, *A*, **157**, 503; Dainton and Norrish, *ibid.*, 1941, *A*, **177**, 393, 411, 421), the methane–oxygen reaction (Norrish and Griffith, *loc. cit.*), and the carbon monoxide–oxygen reaction (Sagulin and Semenoff, *Chem. Reviews*, 1929, **6**, 350). It is exactly parallel to Chamberlain and Walsh's observations (Third Symposium on Combustion, Flame and Explosion Phenomena, Maidson, U.S.A., 1948, p. 368) that small quantities of nitrogen peroxide raised the minimum pressure required for the appearance of cool flames in ethyl ether–oxygen mixtures, whereas it reduced the pressure required for the appearance of the hot flame.

Fig. 3.

Effect of NO_2 *on rate of main reaction.*



Hinshelwood and Williamson ("The Reaction between Hydrogen and Oxygen," Oxford, 1934) attributed the sensitization of the hydrogen–oxygen reaction by nitrogen peroxide to this compound's causing chain branching. This suggestion was developed by Foord and Norrish (*loc. cit.*), and more recently Dainton and Norrish (*loc. cit.*) have shown that chain branching does occur by the reaction between excited HO_2^* radicals and nitrogen peroxide thus:

$$HO_2^* + NO_2 = HO_2 + NO + O \quad . \quad (A4)$$

The oxygen atom produced can, of course, start further chains. Chamberlain and Walsh (*Rev. Inst. franç. Pétr. et Ann. Comb. liquides*, 1948, **4**, 313) have attributed the catalytic effect of nitrogen peroxide on the oxidation of ether and hydrocarbons to the same process. They assume that excited HO_2^* radicals are formed during such oxidation processes. Though we have suggested (Part I) that HO_2 radicals are formed during the low-temperature oxidation of acetaldehyde, we do not regard them as being endowed with any excess energy because in our suggested mechanism these radicals are always produced by a normal metathetical process. An important step, however, in our mechanism is the reaction

$$CH_3{\cdot}CO + O_2 = CH_3{\cdot}CO_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (A2)$$

and this will, of course, give rise to peracetyl radicals endowed with their heat of formation and these are equivalent to the hot HO_2^* radicals shown by Dainton and Norrish to cause chain branching in the hydrogen–oxygen reaction. We attribute the catalytic effect of nitrogen peroxide on the low-temperature oxidation of acetaldehyde to the process

$$CH_3{\cdot}CO_3^* + NO_2 = CH_3{\cdot}CO_3 + NO + O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (A5)$$

The oxygen atom can cause chain branching by reacting with acetaldehyde thus:

$$CH_3{\cdot}CHO + O = CH_3{\cdot}CO + OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (A6)$$

The decrease in the catalytic effect with increasing concentration of nitrogen peroxide (see Fig. 3) may be due to this substance tending to combine with the chain carrier, the acetyl radical; or, more probably, to the excess of nitric oxide produced by reaction (A5) tending to inhibit the chain-branching process by reacting with the active centres. In this connection, it is noteworthy that nitric oxide inhibits the formation of carbon monoxide during the photolysis of acetone, and Anderson and Rollefson (*J. Amer. Chem. Soc.*, 1941, **63**, 816) have attributed this to the following reactions:

$$CH_3{\cdot}CO{\cdot}CH_3 + h\nu = CH_3{\cdot}CO + CH_3$$
$$CH_3{\cdot}CO + NO = CH_3{\cdot}CO{\cdot}NO$$

Rate of Initiation, and Chain Length.—Equation (6) shows that I_a/τ is the rate of initiation. For a particular experiment at 141°, I_a, the initial concentration of nitrogen peroxide, was $1{\cdot}405 \times 10^{-3}$ mole litre^{-1}, and the induction period 195 seconds; hence the rate of initiation is $7{\cdot}2 \times 10^{-6}$ mole litre^{-1} sec.$^{-1}$. Hence, from equation (6a) we can calculate the absolute velocity constant for the initiation reaction. In the above experiment [CH_3·CHO] was $42{\cdot}2 \times 10^{-3}$ mole litre^{-1}, and [O_2] was $41{\cdot}95 \times 10^{-3}$ mole litre^{-1}; hence $k_1 = 0{\cdot}4$ mole litre^{-1} sec.$^{-1}$. With this value of k_1 and the value of 13·8 kcals. for the activation energy of the initiation reaction, we calculate an approximate value of $10^{9{\cdot}35}$ for the frequency factor, A, in the Arrhenius equation $k = Ae^{-E/RT}$.

If we regard the low-temperature oxidation of acetaldehyde as being a simple chain reaction to which we may apply the stationary-state hypothesis, it is possible to estimate, approximately, the chain length. In the stationary state, the rate of initiation r_i equals the rate of chain termination r_t. The overall rate of reaction $R = r_i r_p/r_t = -dP/dt$; hence, since $r_i = r_t$, we have $-dP/dt \approx r_p$. The chain length, r_p/r_i, is therefore $-(dP/dt)/r_i = -(\tau/I_a)(dP/dt)$. In the following table are given values of r_i and $-dP/dt$ for various temperatures and the values for the chain length.

Approximate chain length for the low-temperature oxidation of acetaldehyde.

Temp.	r_i, mm./min.	$-dP/dt$, mm./min.	Chain length.	Temp.	r_i, mm./min.	$-dP/dt$, mm./min.	Chain length.
110°	0·32	0·808	2·5	125·6°	0·62	1·91	3·08
121	0·41	1·54	3·6	141	1·02	2·88	2·82

The chain length of approximately 3 thus derived is very short and is to be compared with the short chains in the liquid-phase oxidation of alcohols by the bisulphite radical ion (Alyea and Bäckström, *loc. cit*), and the low-temperature gas-phase oxidation of acetylene. The similarity between the oxidation of acetaldehyde and acetylene has been discussed previously (Bodenstein, *loc. cit.*; Semenoff, *loc. cit.*). Using Kistiakowsky and Lenher's experimental data (*J. Amer. Chem. Soc.*, 1930, **52**, 3785), Bodenstein derived a chain length of approximately 3 for this reaction also.

Discussion of the Initiation Reaction.—It is obvious from the experiments described above that the reaction between acetaldehyde and oxygen is a radical-chain reaction and that the induction period is due to inhibition by the interaction of nitrogen peroxide, or some compound derived from it, with the active species or chain carrier. The fact that the equation

$$I_a/\tau \approx k_1[\text{Aldehyde}][\text{Oxygen}] \quad \ldots\ldots\ldots \quad (6a)$$

is obeyed, as shown by Fig. 2, proves beyond all reasonable doubt that the chain is initiated by a bimolecular reaction between acetaldehyde and oxygen.

Equation (6a) means that I_a/τ is a measure of the rate of initiation of the oxidation, and the variation of this quantity with temperature will yield a value for the activation energy of the initiation reaction. A plot of the slopes of the straight lines in Fig. 1, *i.e.*, dP_{O_2}/dt against the reciprocal of the absolute temperature, yields a value of 13·8 kcals./mole for the activation energy of the initiation reaction. In Part I it was shown that the overall activation energy for the oxidation of acetaldehyde was 14·2 kcals./mole, a value which has been confirmed by the recent work of Letort and Letort (*Compt. rend.*, 1948, **226**, 77). Hence, most of the activation energy for the overall reaction is due to the initiation reaction as suggested in Part I, and as was shown to be the case for the oxidation of formaldehyde (Axford and Norrish, *Proc. Roy. Soc.*, 1948, *A*, **192**, 518).

As indicated above, we assume the oxidation to be initiated by the reaction (C), and in Part I (*loc. cit.*) we have given evidence to show that such a process would necessarily have an activation energy of between 10 and 20 kcals.

The activation energy for this reaction will, of course, be approximately equal to the difference between the heat of formation of the perhydroxyl radical (HO_2) and the dissociation energy of the aldehydic C–H bond in acetaldehyde. When the previous papers were written neither of these quantities was known with much accuracy, the former being taken as ~60 kcals. (Walsh, *J.*, 1948, 331). Since then more reliable data on the dissociation energy of the functional C–H bond in acetaldehyde have become available. We previously outlined evidence which showed that this was much weaker than any of the other C–H bonds in that molecule, and on this account we indicated that this would be the most likely point of oxygen attack. Further, we were able to show from the then available information that this bond must have a dissociation energy of approximately 70—80 kcals. That the aldehydic C–H bond

is in fact the weakest C–H bond in acetaldehyde has been proved by a mass-spectrometric study of mixtures of normal and deuterated acetaldehydes by Brinton and Blacet (*J. Chem. Physics*, **1949**, **17**, 797). That work, however, does not yield a value for the dissociation energy. From an independent study of the dissociation of acetaldehyde, and other acetyl compounds, by electron impact in a mass-spectrometer (McDowell and Warren, to be published soon) it has been possible to assign a value of between 3 and 3·5 electron volts, *i.e.*, 70—80 kcals. to the dissociation energy of this bond. Some confirmation of these estimates is provided by the value of 80 kcals. obtained by Carson and Skinner (*J.*, **1949**, 936) from a thermochemical study of the hydrolysis of acetyl halides. Thus the previous estimate of the activation energy for the suggested initiation reaction is seen to have been fairly correct and the agreement with the experimental value derived from the results given in the present paper strengthens the arguments in favour of regarding it as the true initiation process for the low-temperature oxidation of acetaldehyde.

UNIVERSITY OF LIVERPOOL. [*Received, January 24th*, 1950.]

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302. *Synthetic Analgesics. Part V. Compounds Related to Pethidine.*

By A. L. MORRISON and H. RINDERKNECHT.

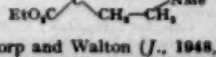
Various substances related to pethidine have been prepared but none was found to be superior in analgesic action.

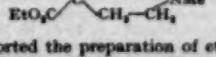
As a continuation of work on synthetic analgesics (Parts I—IV, *J.*, **1944**, 261 *et seq.*) a number of new compounds related to pethidine were prepared several years ago and submitted to pharmacological tests, but none was found to be markedly superior to pethidine (I) in analgesic properties (Macdonald, Wolfe, Bergel, Morrison, and Rinderknecht, *Brit. J. Pharmacol.*, **1946**, **1**, 4).

To simulate the phenolic group in morphine, ethyl 4-(*m*-hydroxyphenyl)-1-methylpiperidine-4-carboxylate was prepared essentially by the method which later came to our knowledge through Report No. PB-981 of the U.S.A. Office of the Publications Board, Department of Commerce. This compound, prepared by the I.G. Farbenindustrie at Hoechst, is known as bemidone. Ethyl 4-(*m*-acetoxyphenyl)-1-methylpiperidine-4-carboxylate was also made by us and characterised as its hydrochloride.

The German workers prepared a number of ketones from 4-cyano-4-phenyl-1-methylpiperidine but seem to have investigated only one of the secondary alcohols which can be derived from them, namely, 4-phenyl-1-methyl-4-(1-hydroxybutyl)piperidine (Report PB-981). These alcohols can be prepared from the ketones either by reduction with sodium and alcohol or, as recently found, by the action of lithium aluminium hydride. 4-Phenyl-1-methyl-4-(1-hydroxyethyl)piperidine and 4-phenyl-1-methyl-4-(1-hydroxypropyl)piperidine and the corresponding acetyl derivatives were prepared. Contrary to the experience of May and Mosettig in the amidone series (*J. Org. Chem.*, **1948**, **13**, 489) where it was found that, although the secondary alcohol obtained by reduction of amidone was inactive, the acetyl derivative was at least as active as the original ketone, it was established that the secondary alcohols were much less active as analgesics than the parent ketones, but that formation of acetyl derivatives did not restore completely the analgesic activity.

Ethyl γ-dimethylamino-α-phenyl-α-methylbutyrate (II), obtained by alcoholysis of the corresponding nitrile, was made to determine if the intact piperidine ring was necessary for full analgesic action in the pethidine series, but it was found to be practically inactive.

(I.) 

 (II.)

Recently Thorp and Walton (*J.*, **1948**, 559) reported the preparation of ethyl 4-phenyl-1-allylpiperidine-4-carboxylate by allylation of norpethidine. This compound, in view of the work of Hart and McCawley (*J. Pharm. Exp. Ther.*, **1944**, **82**, 339) and of Unna (*ibid.*, **1943**, **79**, 27) on *N*-allylnormorphine, had been of interest to us for some time, and it was found that it was readily prepared by alcoholysis of the corresponding nitrile, which could be made either by condensation of 1 : 5-dichloro-3-cyano-3-phenylpentane with allylamine or by condensation of benzyl cyanide with di-(2-chloroethyl)allylamine. The latter compound was readily formed by

the action of thionyl chloride on di-(2-hydroxyethyl)allylamine (Ford-Moore, Lidstone, and Waters, *J.*, 1946, 819) which was made by the action of ethylene oxide on allylamine.

It is well known that in the series of esters of 4-phenyl-1-methylpiperidine-4-carboxylic acid the optimal analgesic effect is found in the ethyl ester (pethidine). It was of theoretical interest to determine if this relationship also held with thio-esters. Ethyl and methyl 4-phenyl-1-methylpiperidine-4-thiocarboxylate were prepared and it was found that, although both were less potent than pethidine itself, the methyl ester was slightly more active than the ethyl ester.

Experimental.

4-Cyano-4-(m-methoxyphenyl)-1-methylpiperidine.—This compound was prepared from *m*-methoxybenzyl cyanide and methyldi-(2-chloroethyl)amine as described in Washington Report PB-981, p. 85, and obtained as an oil, b. p. 134—136°/0·5 mm. It formed a *picrate*, m. p. 231—232° (Found: C, 52·7; H, 4·8; N, 14·8. $C_{20}H_{21}O_9N_5$ requires C, 52·3; H, 4·6; N, 15·3%).

4-(m-Hydroxyphenyl)-1-methylpiperidine-4-carboxylic Acid.—The above nitrile (2 g.) was heated at 120—130° with 60% hydrobromic acid (25 ml.) for 3·5 hours. After cooling, the excess of hydrobromic acid was distilled off under reduced pressure, the solid residue dissolved in water, made alkaline with sodium hydroxide and extracted with ether, and carbon dioxide passed into the aqueous solution, whereupon the acid was obtained as a solid, which, recrystallised from water, had m. p. 329—331° (decomp.) (60%). After drying in a vacuum at 50° over phosphoric oxide for several hours it still contained more than 1 mole of water (Found: C, 60·4; H, 7·1; N, 6·1. Calc. for $C_{13}H_{17}O_3N,H_2O$: C, 61·6; H, 7·5; N, 5·5%).

Ethyl 4-(m-Hydroxyphenyl)-1-methylpiperidine-4-carboxylate.—The above acid (1 g.) was esterified by being heated for 4 hours with a saturated solution of hydrogen chloride in ethanol (60 ml.). The ester was obtained as a solid, m. p. 110°, which was converted into the hydrochloride, m. p. 173—174° (70%) (Found: C, 59·6; H, 7·2; N, 4·8; Cl, 12·0. Calc. for $C_{15}H_{22}O_3NCl$: C, 60·1; H, 7·3; N, 4·7; Cl, 11·8%). Acetylation of the ester with acetic anhydride and pyridine gave the *m*-acetoxy-derivative which gave a *hydrochloride*, m. p. 149—150° (Found: C, 59·4; H, 6·4; N, 3·7. $C_{17}H_{24}O_4NCl$ requires C, 59·7; H, 7·0; N, 4·1%).

4-Phenyl-1-methyl-4-(1-hydroxyethyl)piperidine.—(*a*) To 4-acetyl-4-phenyl-1-methylpiperidine (2 g.), dissolved in ethyl alcohol (50 ml.), was added sodium (4 g.) in small portions, and the solution then heated at 120° for 2 hours. On addition of water and extraction with ether the secondary alcohol was obtained as a solid which, recrystallised from light petroleum (b. p. 60—80°), had m. p. 123·5—124°. (*b*) Reaction of the ketone (7·5 g.) in dry ether (50 ml.) with lithium aluminium anhydride (0·3 g.) during 3 hours in a nitrogen atmosphere gave an 84% yield of the secondary *alcohol* (Found: C, 76·4; H, 9·6; N, 6·9. $C_{14}H_{21}ON$ requires C, 76·7; H, 9·6; N, 6·4%). The *acetate*, prepared by the action of acetic anhydride on a pyridine solution of the alcohol, was a liquid, b. p. 114—116°/0·3 mm. (Found: C, 73·7; H, 8·9; N, 5·4. $C_{16}H_{23}O_2N$ requires C, 73·6; H, 8·8; N, 5·4%).

4-Phenyl-1-methyl-4-(1-hydroxypropyl)piperidine.—A solution of 4-propionyl-4-phenyl-1-methylpiperidine (8 g.) in dry ether (20 ml.) was added to a stirred solution of lithium aluminium hydride (0·25 g.) in dry ether in an atmosphere of nitrogen, and the mixture left at room temperature for 3 hours. When the product was worked up in the usual way the secondary *alcohol* was obtained as a viscous oil, b. p. 125—127°/0·7 mm. (80%) (Found: N, 5·9. $C_{15}H_{23}ON$ requires N, 6·0%). The *acetoxy*-derivative was an oil, b. p. 139—142°/0·8 mm. (Found: C, 74·5; H, 9·75; N, 5·25. $C_{17}H_{25}O_2N$ requires C, 74·2; H, 9·0; N, 5·1%).

Dimethyl-3-cyano-3-phenylbutylamine.—1-Phenylethyl cyanide (13·6 g.) and dimethyl-2-chloroethylamine (10·4 g.) were dissolved in toluene (100 ml.), and powdered sodamide (3·4 g.) was added gradually with stirring. The solution was heated under reflux for 1 hour and after cooling worked up in the normal manner to give the *nitrile* as an oil, b. p. 145—150°/12 mm. (Found: C, 76·9; H, 9·3; N, 13·7. $C_{13}H_{18}N_2$ requires C, 77·3; H, 8·9; N, 13·9%).

Ethyl γ-Dimethylamino-α-phenyl-α-methylbutyrate.—The above nitrile (5 g.) was heated with a mixture of 95% sulphuric acid (4 ml.), water (0·08 ml.), ethyl alcohol (13·9 g.), and ammonium chloride (1 g.) in a sealed tube at 100° for 7 hours. The *ester* was obtained as an oil, b. p. 170—175°/13 mm. (Found: N, 6·1. $C_{15}H_{23}O_2N$ requires N, 5·6%). It formed a crystalline *hydriodide*, m. p. 141—143° (Found: N, 3·75; I^-, 33·7. $C_{15}H_{24}O_2NI$ requires N, 3·7; I^-, 33·7%).

4-Cyano-4-phenyl-1-allylpiperidine.—(*a*) Crude 1:5-dichloro-3-cyano-3-phenylpentane (42 g.), prepared from the corresponding dialcohol (32 g.), was heated with allylamine (35 g.) in methylated spirits (50 ml.) at 130—140° for 8 hours. The basic product gave an oil, b. p. 130—135°/0·5 mm. (70% yield), the *picrate* of which had m. p. 204—205° when recrystallised from alcohol (Found: C, 55·2; H, 4·7; N, 15·4. $C_{21}H_{21}O_7N_5$ requires C, 55·2; H, 4·6; N, 15·0%).

(*b*) Allylamine (12·5 g.) in water (25 ml.) was cooled to 0° and ethylene oxide (30 ml.) gradually added. The sudden rise in temperature could be controlled by addition of ice to the reaction mixture. When all the oxide had been added, the pressure flask was stoppered and left at room temperature for 16 hours. Fractionation of the aqueous solution gave di-(2-hydroxyethyl)allylamine, b. p. 149—150°/15 mm. in 70—80% yield (Found: C, 58·3; H, 10·4; N, 9·3. Calc. for $C_7H_{15}O_2N$: C, 57·9; H, 10·3; N, 9·65%). Condensation of undistilled di-(2-chloroethyl)allylamine (5·4 g.) with benzyl cyanide (3·5 g.) in presence of sodamide (2 g.) in the usual manner gave 4-cyano-4-phenyl-1-allylpiperidine, characterised as its picrate, m. p. 205—206°.

4-Phenyl-1-allylpiperidine-4-carboxylic Acid.—The above nitrile (3 g.) was heated at 135—140° with a mixture of sulphuric acid (5 g.) and water (1 g.) for 1 hour. The reaction mixture was poured into excess of ice-cold sodium hydroxide solution, which was then extracted with ether and saturated with carbon dioxide, whereupon the *acid* was precipitated. After recrystallisation from aqueous alcohol it had m. p. 245—248°. It still contained one mole of water after drying over P_2O_5 (Found: C, 68·3; H, 7·7; N, 5·5%; I^-, 1·06 (Wijs). $C_{15}H_{19}O_2N,H_2O$ requires C, 68·5; H, 8·0; N, 5·3%; I^-, 1).

Ethyl 4-Phenyl-1-allylpiperidine-4-carboxylate.—This ester was made by esterification of the acid, and obtained as an oil, b. p. 130—135°/0·3 mm. It formed a *picrate*, m. p. 134—135°, from alcohol (Found: C, 54·8; H, 5·1; N, 10·75. $C_{22}H_{24}O_9N_4$ requires C, 55·0; H, 5·2; N, 11·2%).

Ethyl 4-Phenyl-1-methylpiperidine-4-thiocarboxylate.—4-Phenyl-1-methylpiperidine-4-carboxyl chloride hydrochloride, prepared from the corresponding acid (5 g.) with thionyl chloride, was added in portions to a well-cooled mixture of ethanethiol (6 g.) and pyridine (4 g.). The mixture was finally refluxed, with carbon dioxide–acetone in the condenser, for 2 hours. The excess of thiol was then driven off with carbon dioxide, an ice-cold solution of sodium hydroxide added, and the mixture extracted with ether. The ethereal solution gave the *thio-ester* as an oil, b. p. 138—139°/0·8 mm. (Found: C, 68·6; H, 8·1; N, 5·2. $C_{15}H_{21}ONS$ requires C, 68·5; H, 8·0; N, 5·3%). The *hydrochloride*, crystallised from acetone, had m. p. 197—200° (Found: Cl^-, 11·3. $C_{15}H_{22}ONCIS$ requires Cl^-, 11·7%). The *methyl* ester was prepared similarly from methanethiol, except that the reaction was carried out in a sealed tube at 80° for 1·5 hours, and was obtained as an oil, b. p. 148—149°/1·5 mm. (Found: C, 67·5; H, 7·6; N, 5·25. $C_{14}H_{19}ONS$ requires C, 67·5; H, 7·6; N, 5·6%). The *hydrochloride* (from acetone) had m. p. 224—226° (Found: Cl^-, 12·0. $C_{14}H_{20}ONSCl$ requires Cl^-, 12·3%).

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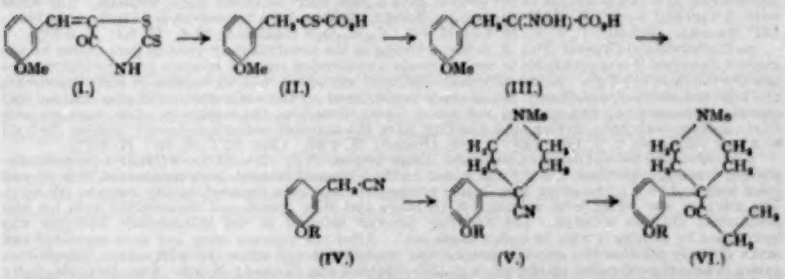
303. *Synthetic Analgesics. Part VI. The Synthesis of Ketobemidone.*

By A. W. D. AVISON and A. L. MORRISON.

Ketobemidone (Hoechst 10720) has been prepared from *m*-methoxybenzyl cyanide by condensing it with methyldi-(2-chloroethyl)amine in the presence of sodamide, submitting the resulting cyanopiperidine derivative to a Grignard reaction, and demethylating the product with hydrobromic acid.

THE analgesic drug, 4-*m*-hydroxyphenyl-1-methyl-4-piperidyl ethyl ketone (VI; R = H), was reported to have been made by Eisleb and his colleagues in the laboratories of the I.G. Farbenindustrie at Hoechst during the war (U.S.A. Office of the Publications Board, Department of Commerce, Report No. PB-981). Under the name ketobemidone (Hoechst No. 10720) it has received pharmacological and clinical investigation (Kirchoff, *Fed. Proc.*, 1948, **7**, 234; Lewis, *J. Pharm. Exp. Ther.*, 1949, **96**, 410; see also *J. Amer. Med. Assoc.*, 1948, **138**, 975), being about ten times as active as pethidine. No details of the synthesis or physical properties of the compound were available at the time of carrying out this work. However, very recently Kägi and Miescher (*Helv. Chim. Acta.*, 1949, **32**, 2489), who refer to F.P. 897,453, which we have been unable to consult, described its preparation by first condensing 3-dimethylamino-1-(*m*-methoxyphenyl)propyl cyanide and 1-chloro-2-bromoethane in the presence of sodamide to give 4-cyano-4-(*m*-methoxyphenyl)-1 : 1-dimethylpiperidinium chloride. This salt was then treated with ethylmagnesium bromide, and methyl chloride removed from the resulting ketone by the action of heat. Demethylation gave (VI; R = H) which the Swiss workers call "Ciradon."



We decided to prepare the ketone by a Grignard reaction on the nitrile (V), which Kägi and Miescher obtained by the action of heat on its methochloride, with suitable protection for the phenolic hydroxyl group.

To prepare *m*-methoxybenzyl cyanide (Chakravati and Rao, *J.*, 1938, 172), necessary for the preparation of (V), we used the rhodanine method starting from *m*-methoxybenzaldehyde (cf. Julian and Sturgis, *J. Amer. Chem. Soc.*, 1935, **57**, 1126). This gave *m*-methoxybenzylidenerhodanine (I) and thence *m*-methoxyphenyl-α-thiopyruvic acid (II) and the oximino-acid (III).

This was not easily isolated in good yield, but the crude product with acetic anhydride underwent dehydration and decarboxylation to give the required *m*-methoxybenzyl cyanide (IV; R = Me) in 52% overall yield from the aldehyde.

Treatment of (IV; R = Me) according to Washington Report PB-981, p. 85, with methyldi-(2-chloroethyl)amine resulted in 4-cyano-4-(*m*-methoxyphenyl)-1-methylpiperidine (V; R = Me). Ethylmagnesium iodide converted this into the ethyl ketone (VI; R = Me) which was readily demethylated with aqueous hydrobromic acid to ketobemidone (VI; R = H).

Experimental.

m-Nitrobenzaldehyde.—When a mixture of potassium nitrate and concentrated sulphuric acid was used for the nitration of benzaldehyde according to Ehrlich (*Ber.*, 1882, **15**, 2010) the reaction mixture tended to set to a hard, boney-like consistency at an early stage, thus preventing stirring and making it impossible to work with more than a few grams at a time. The following method was found satisfactory:

Concentrated sulphuric acid (850 ml.) was treated with concentrated nitric acid (AnalaR; 500 ml.) with cooling. Urea (1·0 g.) was added and the well-stirred mixture cooled to 0°. Pure benzaldehyde (500 g.) was now added at such a rate as to keep the temperature of the reaction mixture between 0° and 5°. After the addition was complete stirring was continued at 5° for 1½ hours. The mixture was then added to crushed ice (*ca.* 2 kg.) and the pale yellow solid which separated filtered and washed thoroughly with water and finally with light petroleum (b. p. 40—60°). The yield of crude *m*-nitrobenzaldehyde after drying was 86% (619 g.). A single recrystallisation from ether–light petroleum sufficed to purify the compound. It had m. p. 57—58° and was identical with the material prepared according to Ehrlich. For large quantities the crystallisation was best carried out with aqueous acetic acid.

m-Methoxybenzaldehyde.—The *m*-nitrobenzaldehyde was reduced in 100-g. batches by the method described in *Org. Synth.* (**25**, 55) and converted into *m*-hydroxybenzaldehyde in yields which were usually below 40%. The latter was methylated according to Lapworth and Shoesmith (*J.*, 1922, 1396).

m-Methoxybenzylidenerhodanine (I).—*m*-Methoxybenzaldehyde (54·4 g.) and rhodanine (53·2 g.) were dissolved in hot glacial acetic acid (265 ml.), and powdered anhydrous sodium acetate (120 g.) added. The mixture was boiled gently under reflux with shaking for 30 minutes. The reaction mixture was poured into cold water (2 l.), and the yellow solid product (92 g., 92%) isolated by filtration and washing with water, alcohol, and finally with ether. The *compound* obtained thus was practically pure, having a m. p. of 227—230°. The analytical specimen crystallised from nitrobenzene in yellow plates, m. p. 229—230° (Found: C, 52·6; H, 3·3; N, 5·7. $C_{11}H_9O_2NS_2$ requires C, 52·6; H, 3·6; N, 5·6%).

m-Methoxyphenyl-α-thiopyruvic acid (II).—The above rhodanine derivative (23 g.) was heated with 15% aqueous sodium hydroxide (117 ml.) on the water-bath until all had dissolved and then for a further 15 minutes. Cooling in an ice–salt mixture and rapid addition of 10% hydrochloric acid (117 ml.) caused the separation of the *acid* as a dark oil which solidified when rubbed to a yellow solid (17·3 g.), m. p. 90—92°. Recrystallisation from *cyclo*hexane raised the m. p. to 98—99° (Found: C, 57·0; H, 4·5; S, 15·1. $C_{10}H_{10}O_3S$ requires C, 57·1; H, 4·8; S, 15·2%).

α-Oximino-β-(m-methoxyphenyl)propionic Acid (III).—Hydroxylamine hydrochloride (10·5 g.) in water (10 ml.) was added to a solution of sodium (3·5 g.) in absolute alcohol (95 ml.). After removal of the sodium chloride by filtration, the solution was added to *m*-methoxyphenyl-α-thiopyruvic acid (10·5 g.) and the mixture boiled for 3 hours. Concentration *in vacuo* gave a semi-solid residue (in subsequent work this was used directly for conversion into the nitrile) which was dissolved in 1·2*N*-sodium hydroxide. Acidification of this solution precipitated the *oxime* as a gum which partly crystallised when rubbed and cooled. Ether-extraction of this semi-solid (leaving some sticky material undissolved) and concentration of the extract gave a gum which solidified under benzene. The white solid (3·9 g.) had m. p. 123—125° (decomp.). Recrystallisation from benzene raised the m. p. to 130—132° (decomp.) (Found: C, 57·8; H, 4·7; N, 7·2. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·2; N, 6·7%).

m-Methoxybenzyl Cyanide (IV; R = Me).—Owing to the unsatisfactory yield of pure oxime by the method described it was preferable to use the crude concentrated reaction mixture from hydroxylamine and the thio-acid (71·5 g.). Acetic anhydride (200 ml.) was added, with ice-cooling at first to moderate the vigorous reaction, and finally the mixture was warmed on the water-bath until effervescence had ceased. Concentrating the resulting solution *in vacuo*, dissolving the residue in ether, washing with dilute sodium carbonate, drying, and distilling gave the required *m*-methoxybenzyl cyanide (29·5 g.) as a pale yellow oil, b. p. 140—145°/12 mm. (Found: N, 9·35. Calc. for C_9H_9ON: N, 9·5%).

4-(*m-Methoxyphenyl*)-1-*methyl*-4-*piperidyl Ethyl Ketone* (VI; R = Me).—4-Cyano-4-(*m*-methoxyphenyl)-1-methylpiperidine (7·0 g.) was added to the Grignard reagent from magnesium (2·9 g.) and ethyl iodide (19·0 g.) [the ether used in this preparation had been replaced by dry benzene (40 ml.)]. The mixture was boiled with stirring for 16 hours and then cooled and decomposed with ice and ammonium chloride solution. The resulting benzene solution of the intermediate ketimine was hydrolysed by heating it with 2*N*-hydrochloric acid. After the aqueous layer had been separated and made strongly alkaline the required ketone was precipitated and extracted with ether. Distillation gave a practically colourless oil (2·6 g.), b. p. 130—134°/0·3 mm. (Found: N, 5·6. Calc. for $C_{15}H_{23}O_2N$: N, 5·4%). Kägi and Miescher give b. p. 126—128°/0·02 mm., m. p. 53—55°.

4-(*m-Hydroxyphenyl*)-1-*methyl*-4-*piperidyl Ethyl Ketone* (*Ketobemidone*) (VI; R = H).—The methyl ether (2·5 g.) was demethylated by boiling it with 48% aqueous hydrobromic acid (20 ml.) for 1 hour. The dark solution was concentrated *in vacuo* and the residue dissolved in absolute alcohol. On addition of an equal volume of dry ether to the hot solution and cooling, the hydrobromide (2·4 g.) of the required hydroxyphenylpiperidine derivative separated in light-brown crystals, m. p. 191—192°. Repeated crystallisation from alcohol–ether (charcoal) increased the m. p. to 193—194° (Kägi and Miescher found m. p. 194—196°) but did not remove all the colour (Found: C, 54·4; H, 6·4; N, 4·5; Br^-, 24·6. Calc. for $C_{14}H_{22}O_2NBr$: C, 54·9; H, 6·7; N, 4·3; Br^-, 24·4%).

This compound was obtained equally well by boiling the crude ketimine from the Grignard reaction with 48% aqueous hydrobromic acid. The hydrobromide (3·85 g.) was dissolved in water (15 ml.) and 2N-ammonia (20 ml.) added to precipitate the free base, a practically white solid (2·2 g.), m. p. 150—151° (Kägi and Miescher give m. p. 155—156°) (Found: N, 5·65. Calc. for $C_{15}H_{21}O_2N$: N, 5·7%). Ketobemidone hydrochloride was made by the action of ethereal hydrogen chloride on the base. It had m. p. 196—197° (Found: C, 63·4; H, 7·6; N, 4·9; Cl^-, 12·5. Calc. for $C_{15}H_{22}O_2NCl$: C, 63·5; H, 7·8; N, 4·9; Cl^-, 12·5%). Kägi and Miescher reported m. p. 197·5—199°.

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304. *Synthetic Analgesics. Part VII. Metadine and Related 3-Phenylpiperidine Derivatives.*

By A. W. D. Avison and A. L. Morrison.

Cyclisation of ethyl 5-chloro-1-amino-2-phenylpentane-2-carboxylate (II), formed by reduction of the corresponding nitrile (I) and methylation of the resulting piperidine derivative, provides an alternative synthesis of ethyl 3-phenyl-1-methylpiperidine-3-carboxylate (metadine), the pethidine isomer previously described (Part IV).

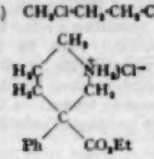
Treatment of metadine with ethylmagnesium iodide produces 3-phenyl-1-methyl-3-piperidyl ethyl ketone (V).

An improved method is described for the preparation of 1-methyl-3-piperidone which was used for the synthesis of 3-propionoxy-3-phenyl-1-methylpiperidine (VI). Neither (V) nor (VI) exceeded metadine in analgesic potency in rats.

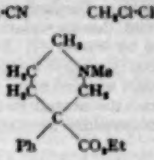
After the preparation of metadine (β-pethidine) (IV) described in Part IV (Bergel, Hindley, Morrison, and Rinderknecht, *J.*, 1944, 269) and the demonstration of its analgesic activity (Glazebrook and Branwood, *Lancet*, 1945, **249**, 528; Macdonald *et al.*, *Brit. J. Pharmacol.*, 1946, **1**, 4) it was decided to make further compounds with the 3-phenylpiperidine skeleton for comparison with the known 4-phenylpiperidines related to pethidine.

The synthesis of metadine itself was previously carried out by the hydrogenation of ethyl 5-benzylmethylamino-α-cyano-α-phenylvalerate. This has now been modified so that the use of the benzylmethylamine is unnecessary. Ethyl 5-chloro-α-cyano-α-phenylvalerate (I) was

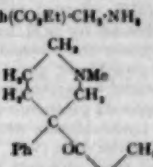
(I.) $CH_2Cl{\cdot}CH_2{\cdot}CH_2{\cdot}CPh(CO_2Et){\cdot}CN$ $CH_2Cl{\cdot}CH_2{\cdot}CH_2{\cdot}CPh(CO_2Et){\cdot}CH_2{\cdot}NH_2$ (II.)



(III.)



(IV.)



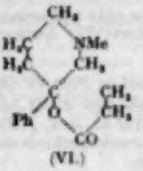
(V.)

reduced in acid solution with hydrogen and palladised charcoal (but not platinum) to the amine (II) which cyclised, slowly on storage or rapidly when heated, to the hydrochloride (III) of ethyl 3-phenylpiperidine-3-carboxylate. The latter base was described in Part IV but the present method of preparation is considerably more satisfactory. Attempted *N*-methylation by catalytic reductive condensation with formaldehyde under the conditions used in the final step of the German synthesis of pethidine (B.I.O.S. Final Report No. 766, p. 60) was unsuccessful. However, methylation proceeded smoothly and in high yield on heating of the base with formaldehyde and formic acid (Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571).

Treatment of metadine with ethylmagnesium iodide gave the ethyl ketone (V) in 60% yield. Similar "incomplete" Grignard reactions on esters have been observed with pethidine derivatives (Ciba Ltd., B.P. 614,567). As was found with the ethyl ketone corresponding to pethidine (Schaumann, *Arch. exp. Path. Pharm.*, 1940, **196**, 109; Macdonald *et al.*, *loc. cit.*) the analgesic potency of (V) was lower than that of metadine.

In view of the high analgesic activity of 4-acyloxy-4-phenylpiperidines (Jensen *et al.*, *Dansk Tidsskr. Farm.*, 1943, **17**, 173; *Chem. Abstr.*, 1945, **39**, 2506; Lee *et al.*, *J. Org. Chem.*, 1947, **12**, 894, 904, 911) it was a necessary part of our programme to investigate the corresponding 3-acyloxy-3-phenyl compounds. Owing to suspension of the work only one such compound

has been made, *viz.*, 3-propionoxy-3-phenyl-1-methylpiperidine (VI). The next lower homologue, 3-acetoxy-3-phenyl-1-methylpiperidine has recently been prepared by McElvain and Vozza (*J. Amer. Chem. Soc.*, 1949, **71**, 896) but not apparently in relation to analgesic studies. Our preparation, though very similar, presents some features worth recording. Ethyl methylaminoacetate was prepared according to Staudt (*Z. physiol. Chem.*, 1925, **146**, 286) by the alcoholysis of the "methylaminoacetonitrile" obtained by reaction between methylamine sulphate, formaldehyde, and potassium cyanide. The high boiling point of the so-called methylaminoacetonitrile obviously pointed to a higher molecular weight than that shown by the simple formulation. Dalgleish and Mann (*J.*, 1947, 658), whose data agree with our own, did not question the structure in spite of an enormous difference in boiling point between ethyl methylaminoacetate and the intermediate nitrile. From its analysis and molecular weight our product would seem to have resulted from condensation of two molecules of methylaminoacetonitrile and one of formaldehyde, presumably having the structure: $CN{\cdot}CH_2{\cdot}NMe{\cdot}CH_2{\cdot}NMe{\cdot}CH_2{\cdot}CN$. Treatment with picric acid or dilute hydrochloric acid gave the salt of methylaminoacetonitrile and liberated formaldehyde. This result is interesting since very recently Cook and Cox (*J.*, 1949, 2334), by a preparation very similar to this, isolated the expected low-boiling monomeric methylaminoacetonitrile together with a high-boiling product which they stated appeared to be derived by condensation of two molecules of formaldehyde with one molecule of methylaminoacetonitrile and also readily yielded salts of the parent substance.



(VI.)

$CO_2Et{\cdot}CH_2{\cdot}NMe{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Et$
(VII.)

Treatment of butyrolactone with hydrobromic acid (Henry, *Compt. rend.*, 1886, **102**, 368; *Ber.*, 1886, **19**, 165R) and esterification of the resulting acid gave a 74% yield of ethyl γ-bromobutyrate, which with ethyl methylaminoacetate (cf. Prill and McElvain, *J. Amer. Chem. Soc.*, 1933, **55**, 1233) afforded the diester (VII). Dieckmann cyclisation of (VII) with powdered sodium, followed by acid hydrolysis and decarboxylation of the resulting cyclic keto-ester following closely the method described by Fuson (*J. Amer. Chem. Soc.*, 1946, **68**, 1239) for 1-methyl-4-piperidone, gave the required 1-methyl-3-piperidone hydrochloride in 86% yield. Thus this seems to represent an altogether simpler route to the piperidone than McElvain and Vozza's improved procedure (*loc. cit.*) and the overall yield is appreciably better. 1-Methyl-3-piperidone hydrochloride with phenylmagnesium bromide and then propionic anhydride and pyridine gave the ester (VI).

Analgesic tests with rats showed that this compound too had a reduced activity compared with metadine, illustrating that the relation between structure and activity does not follow parallel paths in the two series of 3- and 4-phenylpiperidine derivatives. Indeed this is not surprising for metadine itself does not exhibit the other pharmacological effects common to morphine, pethidine, amidone, and their analogues, such as respiratory depression and the characteristic Straub phenomenon in mice. Metadine, on the contrary, stimulates respiration and antagonises the morphine-induced Straub reaction (private communications from Prof. K. Fromherz, Department of Pharmacology, Hoffmann-La Roche, Basle, and Mr. M. W. Parkes of our own laboratories). Its analgesic action (and that of related compounds) may thus be exerted through a mechanism different from that of the morphine-like analgesic drugs.

Experimental.

Ethyl 3-Chloro-α-cyano-α-phenylvalerate (I).—Sodium (5·5 g.) was dissolved in absolute alcohol (240 ml.), and ethyl phenylcyanoacetate (48 g.) added with stirring. 1-Chloro-3-bromopropane (75·4 g.) was run in slowly to the cooled solution and then the mixture was boiled for 9—10 hours. The alcohol and most of the excess of halide were then removed *in vacuo*, the residue was treated with cold water, and the resulting oil taken up in ether. After separation and a further two ether-extractions of the aqueous part, the combined ethereal solutions were washed with two small portions of water, dried, and distilled. The required *cyano*-ester was obtained as a colourless oil (54·9 g., 78%), b. p. 125—127°/0·4 mm. (Found: N, 5·0. $C_{14}H_{16}O_2NCl$ requires N, 5·3%).

Ethyl 3-Phenylpiperidine-3-carboxylate.—Ethyl 3-chloro-α-cyano-α-phenylvalerate (9·9 g.) was hydrogenated in alcohol (110 ml.) with 10% palladised charcoal (5 g.), after addition of alcoholic hydrogen

chloride (20 ml.; 5N.). After absorption of hydrogen was complete the catalyst was filtered off and the solution concentrated *in vacuo*. The residue was dissolved in ice-water and washed twice with ether, and the aqueous solution made strongly alkaline with 30% sodium hydroxide solution. The oil which separated was extracted with ether, dried rapidly, and concentrated. The residue (3·4 g.) became increasingly viscous and was ultimately ether-insoluble. On storage, crystallisation began and was completed by trituration with dry ether. The *ethyl 3-phenylpiperidine-3-carboxylate hydrochloride* (2·5 g.) had m. p. 140° which was increased to 142° on recrystallisation from ethyl acetate (Found: N, 5·6. $C_{14}H_{20}O_2NCl$ requires *N*, 5·2%). The picrate had m. p. 110—111° and did not depress the m. p. of the picrate of authentic material.

Addition of the cyano-ester in portions to an equal weight of catalyst during the hydrogenation improved the yield considerably in this preparation, the product usually being isolated as the free base, b. p. 105°/0·1 mm. Hydrogenation using platinum gave none of the desired product.

Ethyl 3-Phenyl-1-methylpiperidine-3-carboxylate (IV) (*Metadine*).—The above base (4·7 g.) was treated, with cooling, with 98% formic acid (2·5 g.) and then with 40% aqueous formaldehyde (1·8 g.). Warming induced a vigorous evolution of carbon dioxide and the yellow colour at first produced was discharged. The mixture was heated on the water-bath for 4 hours after gas evolution had ceased. It was then cooled, diluted with twice its volume of water, and made strongly alkaline with 30% aqueous sodium hydroxide, with cooling in ice. The oil which separated was extracted with ether, and the extract washed with water, dried, and distilled, to give metadine as a colourless oil (4·4 g.), b. p. 160°/12 mm. n_D^{20} 1·5193 (Found: C, 72·9; H, 8·4; N, 5·8. Calc. for $C_{14}H_{19}O_2N$: C, 72·9; H, 8·3; N, 5·7%).

3-Phenyl-1-methyl-3-piperidyl Ethyl Ketone (V).—Metadine (2·5 g.) was dissolved in dry ether (10 ml.) and added to the Grignard reagent from ethyl iodide (3·2 g.) and magnesium (0·5 g.) in ether (10 ml.). The ether was then replaced by toluene (25 ml.) by distillation and the mixture heated for 5½ hours on the boiling water-bath. After cooling, it was poured on ice, and 2N-hydrochloric acid (20 ml.) added. The layers were separated and the aqueous layer was washed once more with ether and then made strongly alkaline. The resulting oil was extracted 3 times with ether, and the extract dried and distilled. The *ketone* (1·4 g.) was obtained as a colourless oil, b. p. 162—163°/12 mm. (Found: C, 77·2; H, 9·1; N, 6·0. $C_{15}H_{21}ON$ requires C, 77·9; H, 9·15; N, 6·1%).

Ethyl γ-Bromobutyrate.—Butyrolactone (21·5 g.) was dissolved in water (20 ml.) and the solution saturated with gaseous hydrogen bromide in the cold. It was then heated on the water-bath for 1 hour and, with cooling, ether and water were added and the layers separated. The aqueous layer was washed 4 times with ether, and the combined ethereal solutions were washed once with a little water, dried, and concentrated. After being dried thoroughly by dissolution in benzene and repeated distillation *in vacuo*, the residual γ-bromobutyric acid was obtained as a yellow oil (36·7 g.) which set solid on cooling in ice. The crude acid so prepared was next heated with thionyl chloride (35 ml.) under reflux for 2 hours. The excess of thionyl chloride was then removed *in vacuo* and the pale yellow oil thus obtained was treated with absolute alcohol (25 ml.) with good ice-cooling and shaking. When the reaction subsided, the solution was warmed to room temperature, kept for 2 hours, and then poured into ice-water. Extraction of the product with ether gave the required ethyl γ-bromobutyrate as a colourless, fruity-smelling, heavy oil (36·2 g., 74% from the lactone), b. p. 83—85°/13 mm., n_D^{20} 1·4545.

Ethyl Methylaminoacetate.—Crude methylaminoacetonitrile was obtained from methylamine (62 g.) according to the directions of Staudt (*Z. physiol. Chem.*, 1925, **146**, 286) as a light brown oil (120 g.). The bulk of this (80 g.) did not distil below 150°/12 mm. and the low-boiling material was not capable of ready separation into distinct fractions. Continuation of the distillation at 0·1 mm. gave a colourless oil (74·3 g.), b. p. 86—87° (Dalgleish and Mann, *J.*, 1947, 656, give 95—100°/0·2 mm. as the b. p. of "methylaminoacetonitrile") (Found: *N*, 36·1%; *M*, 148. $C_3H_6N_2$ requires N, 36·8%; *M*, 152). The *compound* produced a pronounced odour of formaldehyde on dissolution in dilute hydrochloric acid and gave a picrate, m. p. 141—141·5°, agreeing with that found by Dalgleish and Mann.

Conversion of the distilled nitrile (70 g.) into the hygroscopic crystalline ethyl methylaminoacetate hydrochloride by boiling it with alcoholic hydrogen chloride followed the procedure of Staudt (*loc. cit.*). The free base was best obtained from its salt by suspension in dry ether and passage of dry ammonia according to Prill and McElvain (*J. Amer. Chem. Soc.*, 1933, **55**, 1233), much loss occurring in aqueous solution. The ester (48·5 g.) had b. p. 46—48°/12 mm. It was used immediately for the next step.

1-Methyl-3-piperidone.—The above ester (68 g.) was treated with ethyl γ-bromobutyrate (48·8 g.), and the mixture kept 16 hours at room temperature, a crystalline mass of the sarcosine ester hydrobromide separating. This was filtered off and washed with dry ether, and the combined filtrates were distilled. The tertiary amino-ester (VII) was obtained as a colourless oil (42·5 g.), b. p. 145—147°/12 mm., n_D^{20} 1·4390.

Cyclisation of this compound was based on the method described by Fuson *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 1239) for the preparation of 1-methyl-4-piperidone. The diester (VII) (42·5 g.) was added slowly to powdered sodium (3·9 g.) suspended in xylene (45 ml.) with the preliminary addition of 2 drops of alcohol. Addition to the stirred reaction mixture was carried out at such a rate that a gentle reflux was maintained. After the addition the mixture was boiled gently for a further 45 minutes. It was then cooled and poured into ice-water. The separated xylene layer was further washed with water, and the combined aqueous layers were washed with ether. The aqueous solution was then cooled and acidified (to Congo-red) with concentrated hydrochloric acid below 10°. The solution was neutralised by the addition of solid potassium carbonate and transferred to a separating funnel. Solid potassium carbonate (100 g.) was then added in two portions. The base separated as a red oil which was removed, and the aqueous phase was again treated with potassium carbonate (50 g.) below 10° and extracted twice with ether. The extracts and oil were combined and washed twice with saturated sodium chloride solution (5—10 ml.). The extract was then washed with hydrochloric acid (30 ml. of concentrated acid + 20 ml. of water) in two portions, the acid solution treated with additional concentrated acid (15 ml.), and the dissolved ether removed. It was then boiled until no colour could be observed with ferric chloride (1 hour) and concentrated *in vacuo*. The residue, after drying *in vacuo* with potassium hydroxide pellets, was triturated with dry acetone and filtered, giving the 1-methyl-3-piperidone hydrochloride as a

white solid (23·7 g., 66%), m. p. 110—112° (Prill and McElvain give 110—111°). After a single recrystallisation from alcohol–acetone–ether it melted sharply at 111°.

3-Propionoxy-3-phenyl-1-methylpiperidine (VI).—Phenylmagnesium bromide was prepared by the action of bromobenzene (11·6 g.) on magnesium (1·8 g.) in ether (50 ml.) and to the stirred and cooled solution was added 1-methyl-3-piperidone hydrochloride (5·0 g.). Reaction set in as the mixture was allowed to warm to room temperature, with the separation of a putty-like magnesium complex. The mixture was boiled for 2 hours to complete the reaction and then cooled and decomposed with ice-water and saturated ammonium chloride solution. Distillation of the ethereal extract gave some unchanged piperidone derivative, b. p. 60—70°/12 mm., with the main fraction distilling at *ca.* 70°/0·1 mm. Acylation of the latter with propionic anhydride and pyridine gave a base whose *hydrochloride* had m. p. 190·5° on crystallisation from alcohol–ethyl acetate–ether (Found: C, 63·8; H, 8·3; N, 4·9; Cl^-, 13·0. $C_{15}H_{22}O_2NCl$ requires C, 63·5; H, 7·8; N, 4·9; Cl^-, 12·5%).

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305. *Synthetic Analgesics. Part VIII. Further Attempts to prepare 3-Phenylpiperidine Derivatives.*

By A. W. D. AVISON and A. L. MORRISON.

Some unsuccessful attempts are described to prepare 3-cyano-3-phenyl-1-methylpiperidine which was required for conversion into esters or ketones related to metadine.

In addition, the Mannich reaction with benzyl ketones was studied and found to take place in only one instance, *viz.*, between benzyl methyl ketone, formaldehyde, and methylallylamine. The resulting unsaturated amino-ketone (X), which had weak analgesic properties, could not be converted into a piperidine derivative.

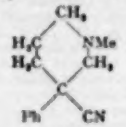
Finally, 3-phenyl-1 : 2-dimethyl-1 : 4 : 5 : 6-tetrahydropyridine has been prepared from the action of methylamine on 1-chloro-4-phenylhexan-5-one.

ORIGINALLY efforts to prepare 3-phenyl-3-piperidyl ketones (see Part VII, preceding paper) were based on many unsuccessful attempts to make a 3-cyano-3-phenylpiperidine for subsequent treatment with a Grignard reagent, and also on the use of the Mannich reaction by means of which the ketone grouping would have been introduced before piperidine ring formation.

1-Chloro-3-bromopropane was condensed with phenylmalononitrile, and the resulting halogen compound (I) treated with benzylmethylamine to give the basic dinitrile (II). Hydrogenation of the latter product proceeded sluggishly and none of the desired piperidine derivative (IV) was obtained.

$$\underset{\text{(I.)}}{CH_2Cl\cdot CH_2\cdot CH_2\cdot CPh(CN)_2} \longrightarrow \underset{\text{(II.)}}{Ph\cdot CH_2\cdot NMe\cdot CH_2\cdot CH_2\cdot CH_2\cdot CPh(CN)_2}$$

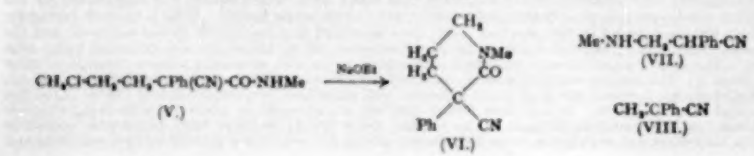
$$\underset{\text{(III.)}}{CH_2Cl\cdot CH_2\cdot CH_2\cdot CPh(CN)\cdot CH_2\cdot OH}$$



(IV.)

Ethyl 3-chloro-α-cyano-α-phenylvalerate (see preceding paper) was next reduced selectively to the cyano-alcohol (III) by means of lithium aluminium hydride. Attempts to replace the hydroxyl with halogen using thionyl chloride or phosphorus tribromide were unsuccessful and (III) itself did not condense with methylamine to give (IV).

Ethyl 3-chloro-α-cyano-α-phenylvalerate reacted readily with aqueous methylamine in the cold to give the methylamide (V) which cyclised in good yield on treatment with sodium ethoxide to form 3-cyano-3-phenyl-1-methyl-2-piperidone (VI). In neither (V) nor (VI) could the amide group be reduced selectively with lithium aluminium hydride.



(V.) (VI.) (VII.) (VIII.)

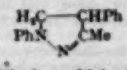
A final attempt in this group required the preparation of 2-methylamino-1-phenylethyl cyanide (VII) by the action of methylamine and formaldehyde on phenylcyanoacetic acid (cf. Mannich and Gans, *Ber.*, **1922**, **55**, 3486). This acid, obtained readily by alkaline hydrolysis of its ethyl ester, had m. p. 74°, not 92° as reported by Hessler who first described the compound (*Amer. Chem. J.*, **1904**, **32**, 127). Reaction with formaldehyde and aqueous methylamine at 0° gave a basic (VII) (hydrochloride, m. p. 160—161°) and a neutral product, the bulk of which polymerised on attempted distillation and which proved to be 1-phenylvinyl cyanide (VIII) formed by decomposition of (VII).

Unfortunately (VII) which was intended to be condensed with 1 : 3-dibromopropane in the presence of sodamide to complete the piperidine ring proved too unstable for this purpose.

It will be apparent that 3-cyano- and 3-carbalkoxy-3-phenylpiperidines and especially 3-phenyl-3-piperidyl ketones may be regarded as Mannich bases. This led to attempts at two other synthetic approaches. First, it was desired to produce a compound such as (IX; X = halogen) which could possibly suffer cyclisation with sodamide. Accordingly, methyl-3-chloropropylamine was prepared from 1-chloro-3-bromopropane and methylamine, but this could not

$CH_2X{\cdot}CH_2{\cdot}CH_2{\cdot}NMe{\cdot}CH_2{\cdot}CHPh{\cdot}CO{\cdot}R$ (IX.)

$CH_2{:}CH{\cdot}CH_2{\cdot}NMe{\cdot}CH_2{\cdot}CHPh{\cdot}CO{\cdot}R$ (X.)

(XI.) 

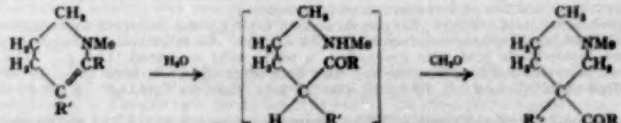
(XII.)

be induced to react with formaldehyde and methyl benzyl ketone in the Mannich reaction. On the other hand methylallylamine condensed readily to give the compound (X; R = Me). The structure of the product was taken to be that shown by virtue of (i) the general rule that $-CH_2-$ is more reactive than CH_3- in a Mannich reaction (Blicke, *Org. Reactions*, **1**, p. 308) and (ii) the colour produced in Feigl and Zappert's test for a methyl ketone (Feigl, "Spot Tests," p. 288). This view was confirmed by treatment with phenylhydrazine which splits out methylallylamine to give the pyrazoline (XI) (cf. Mannich and Bauroth, *Ber.*, **1924**, **57**, 1108; Jacob and Madinaveitia, *J.*, **1937**, **1929**; Levvy and Nisbet, *J.*, **1938**, **1053**; Harradence and Lions, *J. Proc. Roy. Soc. New South Wales*, **1939**, 247). Had the Mannich reaction involved the terminal methyl group, the pyrazoline obtained would have been (XII), but a Kuhn–Roth oxidation showed the presence of a methyl group.

The hydrochloride of (X; R = Me) had slight analgesic activity in the rat. The Mannich product (X; R = Et) from benzyl ethyl ketone and methylallylamine could not be obtained under a variety of conditions. The difficulty of carrying out the Mannich reaction with benzyl ketones (the above is apparently the first example reported) is not readily explained in the absence of a satisfactory theory of the mechanism of this type of condensation. It may be noted that β-tetralone, itself a "benzyl" ketone, was found by Mosettig and May (*J. Org. Chem.*, **1940**, **5**, 528) not to undergo the Mannich reaction with formaldehyde and 1 : 2 : 3 : 4-tetrahydro*iso*quinoline.

All attempts to bring about addition of hydrogen bromide to the double bond of (X; R = Me) in the presence of benzoyl peroxide in the hope of obtaining (IX; R = Me, X = Br) were unsuccessful.

The second type of approach was based on the observation of Lipp (*Ber.*, **1892**, **25**, 2194, 2197; **1905**, **38**, 2276, 2471) that the tetrahydropyridine (XIII; R = Me, R′ = H) on treatment with formaldehyde gave 1-methyl-3-piperidyl methyl ketone (XIV; R = Me, R′ = H). If, in this earliest example of the Mannich reaction, R′ is made Ph, the application to the problem under discussion is obvious.



(XIII.) (XIV.)

In order to obtain the required intermediate (XIII; R′ = Ph, R = Me) 1-cyano-1-phenylpropan-2-one was treated with sodamide and 1-chloro-3-bromopropane to give the chloropropyl compound (XV). Instead of the expected hydrolysis of the nitrile group and consequent

decarboxylation, cleavage took place at the keto-group to give 4-chloro-1-phenylbutyl cyanide. However, it was believed that in view of its somewhat less reactive methylene group a benzyl ketone might be capable of being alkylated with sodamide and 1-chloro-3-bromopropane without giving exclusively a *cyclo*butane derivative as experienced by Case (*J. Amer. Chem. Soc.*,

$CH_2Cl{\cdot}CH_2{\cdot}CH_2{\cdot}CPh(CN){\cdot}COMe$ (XV.)

$CH_2Cl{\cdot}CH_2{\cdot}CH_2{\cdot}CHPh{\cdot}COMe$ (XVI.)

1934, **56**, 715) with benzyl cyanide. This view was confirmed by the preparation of (XVI) by this means, though in rather low yield. Treatment of this 3-chloro-ketone with aqueous methylamine (*cf.* Lipp, *loc. cit.*) gave the required tetrahydropyridine (XIII; R = Ph, R′ = Me). In view of unsatisfactory yields the synthesis was not carried further.

Experimental.

4-Chloro-1 : 1-dicyano-1-phenylbutane (I).—Phenylmalononitrile (7·4 g.) (Hessler, *Amer. Chem. J.*, 1904, **32**, 123) was added with stirring and cooling to a solution of sodium ethoxide (1·2 g. of sodium in 30 ml. of absolute alcohol), followed by 1-chloro-3-bromobutane (8·2 g.) in absolute alcohol (20 ml.). The mixture was then refluxed for 10 hours, sodium bromide separating. It was next concentrated *in vacuo* and the residue treated with ether and water. The ethereal solution together with a further ethereal washing of the aqueous part was washed with water, dried, and concentrated. Distillation gave the *chloro-nitrile* (5·7 g.) as a practically colourless oil, b. p. 111°/0·2 mm. (Found: N, 13·5. $C_{12}H_{11}N_2Cl$ requires N, 12·8%).

4-Benzylmethylamino-1 : 1-dicyano-1-phenylbutane (II).—The above chloro-compound (5·65 g.) was added slowly to a solution of sodium iodide (3·9 g.) in boiling acetone (40 ml.). Benzylmethylamine (6·3 g.) was then added and the reaction mixture boiled under reflux with stirring for 20 hours. After concentration *in vacuo* and treatment of the residue with excess of 2*N*-sodium hydroxide with cooling, the product was extracted with ether. The extract was washed, dried, and concentrated, and the residue distilled, to give the basic *nitrile* (5·0 g.), a pale golden-brown syrup, b. p. 156—157°/0·3 mm. (Found: C, 78·6; H, 6·6; N, 13·4. $C_{26}H_{25}N_3$ requires C, 79·2; H, 6·9; N, 13·9%).

This material absorbed hydrogen only slowly and incompletely in the presence of palladised charcoal giving rise to a non-homogeneous high-boiling product which was not investigated.

5-Chloro-2-cyano-2-phenylpentan-1-ol (III).—A solution of lithium aluminium hydride (2·3 g.) in dry ether (130 ml.) was added slowly under dry nitrogen to a stirred ethereal solution of ethyl 5-chloro-α-cyano-α-phenylvalerate (26·6 g. in 70 ml.). After the vigorous reaction had subsided the reaction mixture was cooled in ice and treated cautiously with cold 2*N*-sulphuric acid until strongly acid. The layers were separated, the aqueous layer was washed once with ether, and the combined ethereal extracts were washed with water and dried. The *cyano-alcohol* was obtained as a clear syrup (22·5 g.) on concentrating the ethereal solution and carefully drying it *in vacuo* (Found: Active H, 1·0 atom per mole. $C_{19}H_{20}ONCl$ requires Active H, 1·0 atom per mole). Attempts at distillation at 0·5 mm. usually resulted in decomposition and distillates giving inconsistent analyses, although in some cases distillation was possible giving a pale yellow oil of b. p. 155—159°/0·5 mm. (Found: N, 4·2; Cl, 13·4. $C_{19}H_{20}ONCl$ requires N, 4·0; Cl, 15·9%).

Treatment of this compound with thionyl chloride or phosphorus tribromide in the presence of tertiary bases gave none of the desired halogenated products.

Reaction with methylamine at 140° for 8 hours did not yield any piperidine derivative.

N-Methylamide of 5-Chloro-α-cyano-α-phenylvaleric Acid (V).—Ethyl 5-chloro-α-cyano-α-phenylvalerate (13·3 g.) was shaken with aqueous methylamine solution (30 ml. of 33%) for 3 hours. The *N-methylamide* separated as a white solid (10·1 g.), m. p. 100—104°. Recrystallisation from benzene–light petroleum (b. p. 40—60°) raised the m. p. to 105—110° (Found: C, 62·3; H, 6·1; N, 10·6. $C_{13}H_{15}ON_2Cl$ requires C, 62·3; H, 6·0; N, 11·1%).

3-Cyano-3-phenyl-1-methyl-2-piperidone (VI).—The above amide (26·5 g.) dissolved in alcohol (120 ml.) was added to sodium ethoxide from sodium (2·4 g.) and alcohol (60 ml.), and the solution heated to gentle reflux on the water-bath for 1½ hours. After cooling and filtration from the separated sodium chloride, the alcoholic solution was concentrated and the residue dissolved in ethyl acetate. The extract was washed twice with water and distilled. The *piperidone* derivative (18·7 g.) was collected as a colourless, viscous syrup, b. p. 167—170°/0·2 mm. (Found: C, 73·3; H, 7·0; N, 12·7. $C_{13}H_{14}ON_2$ requires C, 72·9; H, 6·6; N, 13·0%).

Attempted selective reduction of (V) or (VI) with lithium aluminium hydride gave only mixtures of basic products from which a pure compound was not isolated.

Phenylcyanoacetic Acid.—Ethyl phenylcyanoacetate (18·9 g.) was dissolved in 2*N*-aqueous sodium hydroxide (100 ml.) and kept at room temperature for 6 hours. On acidification (Congo-red paper) with concentrated hydrochloric acid with ice-cooling, a white solid separated (13·9 g.). The analytical specimen was recrystallised from benzene and then from ether–light petroleum (b. p. 40—60°), whereafter it melted at 74° (Found: C, 66·9; H, 4·9; N, 8·7. Calc. for $C_9H_7O_2N$: C, 67·0; H, 4·4; N, 8·7%).

2-Methylamino-1-phenylethyl Cyanide (VII).—Phenylcyanoacetic acid (13·5 g.) was treated with 33% aqueous methylamine (7·8 ml.) with cooling in ice and then with 40% formaldehyde solution (6·3 ml.), slight carbon dioxide evolution occurring. The mixture was kept close to 0° for 24 hours, whereafter the smells of methylamine and formaldehyde had disappeared. Addition of 2*N*-hydrochloric acid (30 ml.) then caused vigorous evolution of carbon dioxide. The acidified reaction mixture was extracted twice with ether to remove non-basic material, the aqueous part made alkaline with 2*N*-aqueous ammonia (60 ml.), and the oil which was precipitated was extracted by washing 4 times with ether. The ethereal

solutions were washed with water, dried, and concentrated to give the required base as a pale yellow oil (4·9 g.) with an ammoniacal smell. This crude base was converted into the *hydrochloride*, m. p. 160—161° (Found: C, 61·4; H, 6·9; N, 14·3. $C_{16}H_{18}N_4Cl$ requires C, 61·0; H, 6·6; N, 14·2%), by taking it up in ether and treating it with excess of alcoholic hydrogen chloride. Recrystallisation was from absolute alcohol.

1-*Phenylvinyl Cyanide* (VIII).—This *compound* was isolated from the above reaction mixture by washing the ethereal extract of non-basic substances with dilute sodium carbonate solution and then with water. Drying and concentration of the extract gave a pale yellow oil (4·8 g.). On attempted distillation only a few drops of colourless oil, b. p. *ca.* 100°/12 mm., could be obtained (Found: N, 10·9. C_9H_7N requires N, 10·9%). The residue would not distil, merely becoming increasingly viscous without appreciable darkening as the temperature was raised.

1-*Allylmethylamino-2-phenylbutan-3-one* (X; R = Me).—Benzyl methyl ketone (13·4 g.) was dissolved in absolute alcohol (30 ml.) and mixed with allylmethylamine (7·8 g.) dissolved in alcoholic hydrogen chloride (10 ml.). Paraformaldehyde (3 g.) was added and the mixture refluxed for 1 hour, a further quantity (3 g.) of paraformaldehyde being then added and the refluxing continued for 3½ hours longer. Concentration of the reaction mixture under reduced pressure gave a pasty solid which was triturated with acetone (50 ml.) and filtered off. The white solid (11·7 g.) had m. p. 145—150° and, on recrystallisation from acetone–alcohol, the pure *hydrochloride* melted sharply at 160° (Found: C, 66·5; H, 7·7; N, 5·4; Cl, 13·7. $C_{14}H_{20}ONCl$ requires C, 66·3; H, 7·9; N, 5·5; Cl, 14·0%). The recrystallised product gave a pale violet colour when subjected to Feigl and Zappert's test for a methyl ketone (Feigl, "Spot Tests," p. 289).

1 : 4-*Diphenyl*-3-*methyl*-Δ^4-*pyrazoline* (XI).—The above hydrochloride (3 g.) was treated with anhydrous sodium acetate (3 g.) and phenylhydrazine (3 g.) in a mixture of absolute alcohol (10 ml.) and glacial acetic acid (10 ml.) according to the procedure of Levvy and Nisbet (*J.*, 1938, 1033). Sodium chloride was filtered off and the resulting solution boiled gently for 7 hours under reflux. After 4 days at ordinary temperature crystals separated. These were collected and recrystallised from methanol. The *pyrazoline* was obtained as yellow plates, m. p. 159—160° (Found: N, 12·6; *C*-Me, 7·8. $C_{16}H_{16}N_2$ requires N, 11·9; *C*-Me, 6·4%).

Action of Hydrogen Bromide on (X; R = Me).—The hydrochloride of (X; R = Me) (1·75 g.) was suspended in carbon tetrachloride (125 ml.), and benzoyl peroxide (0·06 g.) added. The mixture was then saturated with dry hydrogen bromide and left for 14 days. It was then boiled for 3 hours and filtered. The solid (1·95 g.) had m. p. 158—161°. On recrystallisation from alcohol the *hydrobromide* of (X; R = Me) was obtained with m. p. 166° (Found: C, 56·6; H, 6·8; N, 4·9. $C_{14}H_{20}ONBr$ requires C, 56·7; H, 6·7; N, 4·7%).

A modification of the above procedure using the free Mannich base dissolved in benzene was tried. In the presence of a trace of benzoyl peroxide, dry hydrogen bromide was passed over the surface of the gently boiling solution. Once again, only unsaturated hydrobromide could be isolated.

Methyl-3-chloropropylamine.—1-Chloro-3-bromopropane (15·9 g.) and 26% alcoholic methylamine (24 ml.) were mixed with ice-cooling and then kept at room temperature for 16 hours. Considerable separation of methylamine hydrobromide had taken place and this was completed by addition of dry ether. The filtered solution was then treated with dry hydrogen chloride and concentrated under reduced pressure. The residue was dried in a vacuum over phosphoric oxide and then suspended in dry ether–acetone, filtered very rapidly, and transferred to a desiccator. The *methyl-3-chloropropylamine hydrochloride* was extremely hygroscopic and a melting point was not determined (Found: Cl^-, 23·8. $C_4H_{11}NCl_2$ requires Cl^-, 24·6%).

This hydrochloride was treated with formaldehyde and benzyl methyl ketone as described for the *N*-allyl compound but no crystalline products were obtained. The result was equally unsatisfactory when an aqueous medium was employed (cf. Mannich and Braun, *Ber.*, 1920, **53**, 1875).

Condensation of 1-*Cyano*-1-*phenylpropan*-2-*one and Trimethylene Chlorobromide*.—1-Chloro-3-bromopropane (23·7 g.) was added to the sodio-derivative from 1-cyano-1-phenylpropan-2-one (*Org. Synth.*, **18**, 66) (12·0 g.) and sodamide (3·0 g.) in dry toluene (100 ml.). The mixture was heated under reflux with stirring for 30 hours. It was then cooled and washed thoroughly with cold water. The toluene solution was then concentrated and the residue distilled, a fraction (5·0 g.) boiling at 120—140°/0·2 mm. being collected. This pale yellow, viscous oil (XV) was subjected to hydrolysis by boiling for 10 hours with 20% sulphuric acid, and the product characterised by condensation with dimethylamine. The 4-dimethylamino-1-phenylbutyl cyanide was an oil, giving a *picrate*, m. p. 109—110° (Found: C, 52·9; H, 5·0; N, 16·5. $C_{11}H_{14}N_2,C_6H_3O_7N_3$ requires C, 52·9; H, 4·9; N, 16·5%).

1-*Chloro*-4-*phenylhexan*-3-*one* (XVI).—Benzyl methyl ketone (10·0 g.) and 1-chloro-3-bromopropane (11·7 g.) were dissolved in dry toluene (50 ml.), and powdered sodamide (3·0 g.) added with stirring and cooling. The orange-coloured solution was stirred at room temperature for 1½ hours and then heated gradually to the b. p. (3 hours) and kept there for 1 hour. The mixture was cooled and poured into water. The toluene solution was washed thoroughly with water and concentrated. Distillation gave rise to the required ketone (2·5 g.) as the fraction, b. p. *ca.* 146°/12 mm., giving a 2 : 4-*dinitrophenylhydrazone*, m. p. 116—117° (Found: C, 54·8; H, 4·6; N, 14·4. $C_{18}H_{17}O_4N_4Cl$ requires C, 55·2; H, 4·8; N, 14·4%).

3-*Phenyl*-1 : 2-*dimethyl*-1 : 4 : 5 : 6-*tetrahydropyridine* (XIII; R = Me, R′ = Ph).—The above chloro-ketone (2·4 g.) was treated with 33% aqueous methylamine (5·5 ml.) and alcohol (10 ml.). The mixture was heated in a sealed tube for 16 hours at 140°. The basic product gave a very hygroscopic *hydrochloride* which could not be recrystallised successfully (Found: C, 67·7; H, 8·0; N, 5·7. $C_{13}H_{18}NCl,\frac{1}{2}H_2O$ requires C, 67·1; H, 8·1; N, 6·0%).

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306. *Synthetic Analgesics. Part IX. Synthesis of Compounds Related to Amidone.*

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Two compounds in the amidone series, 1-methylallylamino-3 : 3-diphenylhexan-4-one and 1-diallylamino-3 : 3-diphenylhexan-4-one have been prepared but found to possess slight analgesic action. A new synthesis of 3-dimethylamino-1 : 1-diphenylbutyl cyanide (amidone nitrile) is described.

In attempts to prepare the nitroso-derivative of the substance formed by hydrogenation of 3-benzhydrylmethylamino-1 : 1-diphenylpropyl cyanide, 3 : 3-diphenyl-1-methylpyrrolid-2-one was isolated.

The preparation of amidone was first described in Report No. PB-981, U.S.A. Office of the Publication Board, Department of Commerce, and more recently an improved synthesis of the intermediate 3-dimethylamino-1 : 1-diphenylbutyl cyanide has been reported by Schultz, Robb, and Sprague (*J. Amer. Chem. Soc.*, 1947, **69**, 2454).

In the preparation of amidone from this nitrile by treatment with ethylmagnesium iodide in toluene, it was found that, when the toluene solution of the Grignard reaction mixture was decomposed by warm 2*N*-sulphuric acid, amidone sulphate separated and after cooling could be filtered off in at least 90% yield.

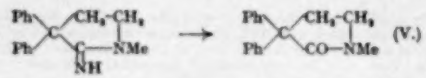
It was early recognised that one of the disadvantages of amidone was the definite depressant effect it exerted on respiration. We considered, in view of the work of Hart and McCawley (*J. Pharm. Exp. Ther.*, 1944, **82**, 339) and of Unna (*ibid.*, 1943, **79**, 27) on *N*-allylnormorphine, that it would be of interest to make and test substances of the amidone series which carried allyl groups on the nitrogen atom.

Benzhydryl cyanide and ethylene dichloride in presence of sodamide gave 3-chloro-1 : 1-diphenylpropyl cyanide (I) (Dupré, Elks, Hems, Speyer, and Evans, *J.*, 1949, 500) which, when heated with methylallylamine, gave 3-methylallylamino-1 : 1-diphenylpropyl cyanide (II; R = Me, R′ = CH_2·CH:CH_2), whence ethylmagnesium iodide afforded 1-methylallylamino-

$$\underset{\text{(I.)}}{Ph_2C(CN)\cdot CH_2\cdot CH_2Cl} \qquad \underset{\text{(II.)}}{Ph_2C(CN)\cdot CH_2CH_2\cdot NRR'} \xrightarrow{C_2H_5\cdot MgI} \underset{\text{(III.)}}{Ph_2C(COEt)\cdot CH_2\cdot CH_2\cdot NRR'}$$

3 : 3-diphenylhexan-4-one (III; R = Me, R′ = CH_2·CH:CH_2). In a similar manner from diallylamine, 3-diallylamino-1 : 1-diphenylpropyl cyanide (II; R = R′ = CH_2·CH:CH_2), and 1-diallylamino-3 : 3-diphenylhexan-4-one (III; R = R′ = CH_2·CH:CH_2) were prepared. Methylallylamine was obtained most readily by applying the method of Decker and Becker (*Annalen*, 1913, **395**, 362) to unsaturated amines.

Two other methods of preparing compounds of type (III; R = Me, R′ = CH_2·CH:CH_2) were tried. Benzhydrylmethyl-2-chloroethylamine, obtained by chlorination of benzhydrylmethyl-2-hydroxyethylamine, was condensed with benzhydryl cyanide to give 3-benzhydrylmethylamino-1 : 1-diphenylpropyl cyanide (II; R = Me, R′ = $CHPh_2$). Although previous work had shown that it was not practicable to remove a benzyl group from a tertiary amine and leave a nitrile group in the same molecule unaffected (cf. Bergel, Hindley, Morrison, and Rinderknecht, *J.*, 1944, 269), it was hoped in view of work described in B.P. 607,772 that this would be possible where a benzhydryl group was involved. Hydrogenation of (II; R = Me, R′ = $CHPh_2$) proceeded slowly and gave a small amount of product, b. p. 155—160°/0·3 mm., which on addition of 2*N*-hydrochloric acid gave a crystalline hydrochloride, m. p. 226—228°. Heating an aqueous solution of this salt with potassium nitrite gave a neutral product, m. p. 146—148°, which instead of the expected nitroso-derivative proved to be 3 : 3-diphenyl-1-methylpyrrolid-2-one (V). The formation of this compound can be explained by the intermediate formation of 2-imino-3 : 3-diphenyl-1-methylpyrrolidine (IV), which has not been characterised.



The alternative method considered for the preparation of (III; R = Me, R′ = CH_2·CH:CH_2) was to hydrogenate the quaternary bromide obtained from allyl bromide and 1-benzylmethylamino-3 : 3-diphenylhexan-4-one (III; R = Me, R′ = CH_2Ph) (Dupré *et al.*, *loc. cit.*) so as to remove the benzyl group. Hydrogenation of the quaternary salt with palladium–barium

sulphate catalyst and 1 mole of hydrogen gave a product which could be separated into two fractions on distillation at 0·1 mm. Fraction 1 had b. p. 146°/0·1 mm. and analysed as 1-methylallylamino-3 : 3-diphenylhexan-4-one (III; R = Me, R′ = CH_2·CH·CH_3) or 1-methylpropylamino-3 : 3-diphenylhexan-4-one (R = Me, R′ = Pr^n), while fraction 2 had b. p. 190—190°/0·1 mm. and analysed as 1-benzylmethylamino-3 : 3-diphenylhexan-4-one (III; R = Me, R′ = CH_2Ph). This result indicates that an allyl group is just as susceptible to hydrogenolysis as a benzyl group (cf. Howton, *J. Amer. Chem. Soc.*, 1947, **69**, 2555).

The original German method for synthesising amidone involves a considerable waste of material, as at least two isomeric nitriles are formed in the reaction of the base from 2-chloropropyldimethylamine hydrochloride and benzhydryl cyanide, only one of which gives amidone. In a search for a more economical preparative method for amidone nitrile we explored the possibilities of the following synthesis: Benzhydryl cyanide was condensed with 1-chloro-2 : 2-diethoxyethane to give 2-cyano-2 : 2-diphenylpropaldehyde diethyl acetal (VI), which on acid hydrolysis gave the corresponding aldehyde (VII), characterised by its azine. Treatment of (VII) with 1 mole of methylmagnesium iodide gave a product b. p. 154—156°/0·1 mm., which analysed correctly for the expected secondary alcohol (VIII). It might be expected that the product should be 2-imino-3 : 3-diphenyl-5-methyltetrahydrofuran, as prepared by Easton, Gardner, and Stevens (*J. Amer. Chem. Soc.*, 1947, **69**, 2941) by the condensation of benzhydryl cyanide and propylene oxide, but we did not obtain it crystalline as reported. On treatment with thionyl chloride in presence of dimethylaniline, a crude chloro-compound was obtained which on condensation with dimethylamine gave a small yield of 3-dimethylamino-1 : 1-diphenylbutyl cyanide, isolated and identified as its picrate.

$Ph_2C(CN)$·CH_2·CH$(OEt)_2$ (VI.) $Ph_2C(CN)$·CH_2·CHO (VII.) $Ph_2C(CN)$·CH_2·CHMe·OH (VIII.)

When tested for analgesic action (III; R = Me, R′ = CH_2·CH·CH_3) and (III; R = R′ = CH_2·CH·CH_3) had respectively one-half and one-eighth of the potency of (III; R = R′ = Me).

Experimental.

2-Dimethylamino-4 : 4-diphenylheptan-5-one (Amidone).—When the toluene solution of the Grignard complex from ethylmagnesium iodide and 3-dimethylamino-1 : 1-diphenylbutyl cyanide was heated with excess of 2*N*-sulphuric acid on the water-bath for 30 minutes, amidone sulphate crystallised out on cooling. It was filtered off and suspended in water, and excess of sodium hydroxide solution added to liberate the free base which was taken up in ether. After drying of the ethereal solution, amidone hydrochloride was formed by addition of alcoholic hydrogen chloride and obtained pure (m. p. 232—233°) in 91% yield (Found: C, 72·8; H, 8·0; N, 4·4. Calc. for $C_{21}H_{28}ONCl$: C, 72·95; H, 8·1; N, 4·05%).

3-Methylallylamino-1 : 1-diphenylpropyl Cyanide (II; R = Me, R′ = CH_2·CH·CH_3).—3-Chloro-1 : 1-diphenylpropyl cyanide (14·8 g.), sodium iodide (8·7 g.), and methylallylamine (13 ml.) in methanol (30 ml.) were heated in a pressure-bottle for 36 hours at 100°. On working up of the product for basic material the *cyanide* was obtained as an oil, b. p. 152°/0·3 mm. (6·5 g.) (Found: C, 82·1; H, 7·6; N, 10·1. $C_{20}H_{22}N_2$ requires C, 82·8; H, 7·6; N, 9·6%).

1-Methylallylamino-3 : 3-diphenylhexan-4-one (III; R = Me, R′ = CH_2·CH·CH_3).—To a Grignard solution in dry benzene (50 ml.), prepared from magnesium (3·7 g.) and ethyl iodide (17·8 g.), was added the above cyanide (6·5 g.), and the solution heated under reflux for 16 hours. The product was then heated on the boiling water-bath with a solution of concentrated hydrochloric acid (75 ml.) in water (250 ml.) for 3½ hours. The aqueous portion was then made alkaline and the base extracted with ether. After drying and concentration of the ethereal solution the *ketone* was obtained as an oil, b. p. 158°/0·5 mm. (6·2 g.) (Found: C, 82·5; H, 8·4; N, 4·7. $C_{23}H_{27}ON$ requires C, 82·3; H, 8·4; N, 4·4%). It forms a *methiodide*, m. p. 160—161° (Found: N, 3·2. $C_{24}H_{30}ONI$ requires N, 3·0%).

3-Diallylamino-1 : 1-diphenylpropyl Cyanide (II; R = R′ = CH_2·CH·CH_2).—3-Chloro-1 : 1-diphenylpropyl cyanide (7 g.) and diallylamine (12 ml.) in ethyl alcohol (15 ml.) were heated at 155° for 16 hours under pressure. On being worked up as previously described, the *cyanide* (4·6 g.) was obtained as an oil, b. p. 162—163°/0·5 mm. (Found: C, 82·6; H, 7·1; N, 9·2. $C_{22}H_{24}N_2$ requires C, 83·5; H, 7·6; N, 8·9%).

1-Diallylamino-3 : 3-diphenylhexan-4-one (III; R = R′ = CH_2·CH·CH_2).—From the above cyanide the *ethyl ketone* was obtained in the normal manner as an oil, b. p. 154°/0·2 mm., in about 50% yield (Found: C, 82·65; H, 8·3; N, 4·3. $C_{24}H_{29}ON$ requires C, 83·0; H, 8·4; N, 4·0%).

Methylallylamine.—Allylamine (22·8 g.) was slowly mixed with benzaldehyde (44·5 g., 1·05 moles), ether was added, and the water formed was separated. The residue was dried by distilling off benzene and then heated with methyl iodide (75 g., 1·3 moles) in a pressure-bottle at 80° for 16 hours. The dark viscous oil which was formed became crystalline and was triturated with benzene, and the solid filtered off with exclusion of moisture. The solid was then decomposed with water, and the aqueous portion, after being thoroughly extracted with ether, concentrated to a smaller volume and made alkaline with 50% sodium hydroxide solution. The methylallylamine which separated had b. p. 62—64° and weighed 20·1 g. (71%). When the base was prepared by decomposition of the quaternary salt from allyl bromide and the Schiff's base from methylamine and benzaldehyde, the yield was only 14%.

Benzhydrylmethyl-2-hydroxyethylamine.—A mixture of benzhydrylmethylamine (25·9 g.) and ethylene oxide (6 g.) was heated in a closed vessel at 100° for 24 hours and the product then distilled to give the

alcohol as an oil, b. p. 145—148°/0·4 mm. (27·7 g.) (Found: C, 80·6; H, 9·1; N, 5·1. $C_{16}H_{17}ON$ requires C, 79·7; H, 7·0; N, 5·8%).

Benzhydrylmethyl-2-chloroethylamine Hydrochloride.—The above alcohol (27·7 g.) was dissolved in chloroform (85 ml.), and thionyl chloride (17 g.) added slowly with cooling and shaking. The mixture was heated under reflux for 2 hours, some of the chloroform and the excess of thionyl chloride were then distilled off, and acetone was added to the residue, whereupon the *hydrochloride* crystallised. Recrystallised from chloroform–acetone it melted at 193—195° (Found: Cl′, 12·0. $C_{16}H_{19}NCl_2$ requires Cl′, 12·0%).

3-*Benzhydrylmethylamino*-1 : 1-*diphenylpropyl Cyanide* (II; R = Me, R′ = $CHPh_2$).—To a solution of benzhydryl cyanide (9·6 g.) and benzhydrylmethyl-2-chloroethylamine base (liberated from 16·5 g. of its hydrochloride) in dry toluene (150 ml.), sodamide powder (2·0 g.) was added and the reaction mixture refluxed for 2 hours with vigorous stirring. After cooling it was extracted 3 times with 2*N*-hydrochloric acid. The aqueous part and the insoluble hydrochloride of the reaction product were treated with 50% sodium hydroxide solution, the freed base was extracted with ether, and the ethereal extract washed with water, dried (Na_2SO_4), and evaporated. The residue was distilled in a high vacuum to give the *cyanide* (9 g.) as a resinous, amber-coloured substance, which solidified and after two recrystallisations from light petroleum (b. p. 60—80°) melted at 120—123° (Found: C, 85·9; H, 6·6; N, 6·8. $C_{29}H_{28}N_2$ requires C, 86·6; H, 6·7; N, 6·7%).

3 : 3-*Diphenyl*-1-*methylpyrrolid*-2-*one*.—The above nitrile (4·2 g.) dissolved in warm alcohol was shaken with a palladium–barium sulphate catalyst (prepared *in situ* from 0·4 g. of barium sulphate and 0·5 ml. of 10% palladium chloride solution) in presence of hydrogen. The uptake of hydrogen proceeded slowly until 0·8 mole had been absorbed, whereafter it ceased. The alcoholic solution was then filtered, made acid, and evaporated to dryness, and the residue dissolved in water and extracted with ether to remove the diphenylmethane formed. The aqueous portion was made alkaline and extracted with ether, and the extracted base distilled at 155—160°/0·3 mm. (1·6 g.). This base, when treated with 2*N*-hydrochloric acid, gave a hydrochloride, m. p. 226—228°, analysis of which (C, 67·6; H, 7·2; N, 10·7%) did not agree with the theoretical values for 3-methylamino-1 : 1-diphenylpropyl cyanide (II; R = Me, R′ = H) hydrochloride, or, of course, for the isomeric 2-imino-3 : 3-diphenyl-1-methylpyrrolidine hydrochloride. In an attempt to make a nitroso-derivative of (II; R = Me, R′ = H), an aqueous solution of the hydrochloride, m. p. 226—228°, was heated with potassium nitrite, whereupon a neutral substance, m. p. 146—148° [from light petroleum (b. p. 60—80°)], was formed. This compound, from its properties and analysis, would appear to be 3 : 3-diphenyl-1-methylpyrrolid-2-one (Dupré *et al.*, *loc. cit.*) (Found: C, 80·8; H, 6·7; N, 5·2. Calc. for $C_{17}H_{17}ON$: C, 81·3; H, 6·8; N, 5·6%).

Benzylmethylallyl-4-*keto*-3 : 3-*diphenylhexylammonium Bromide*.—Reaction of 1-benzylmethylamino-3 : 3-diphenylhexan-4-one in ether with allyl bromide gave the quaternary *salt*, m. p. 171—174° (from acetone) (Found: C, 70·4; H, 6·9; N, 2·8. $C_{29}H_{34}ONBr$ requires C, 70·8; H, 6·9; N, 2·8%).

Hydrogenation of this salt (1·8 g.) in alcohol with freshly prepared palladium–barium sulphate (0·1 g.) proceeded slowly until 1 mole of hydrogen (90 ml.) had been absorbed, then becoming much slower. The hydrogenation was interrupted and the alcohol distilled off. The residue was treated with 2*N*-sodium hydroxide and extracted with amyl alcohol. The amyl-alcoholic extract was washed and distilled. The product was obtained as a thick oil which gave two fractions: (i) b. p. 146°/0·1 mm., and (ii) b. p. 180—190°/0·1 mm. From its analysis the first fraction may be 1-methylallylamino-3 : 3-diphenylhexan-4-one or 1-methylpropylamino-3 : 3-diphenylhexan-4-one (Found: C, 82·0; H, 8·8; N, 4·0. Calc. for $C_{22}H_{27}ON$: C, 82·2; H, 8·4; N, 4·4%). The second fraction analysed as 1-benzylmethylamino-3 : 3-diphenylhexan-4-one (Found: C, 83·8; H, 8·0; N, 3·9. Calc. for $C_{26}H_{29}ON$: C, 84·1; H, 7·8; N, 3·8%).

2-*Cyano*-2 : 2-*diphenylpropaldehyde Diethyl Acetal* (VI).—To benzhydryl cyanide (5·0 g.) and chloroacetaldehyde diethylacetal (4·0 g.) in dry benzene (30 ml.) sodamide (1·1 g.) was added, with stirring, and the mixture then refluxed for 2 hours. The benzene solution was well washed with water, the benzene distilled off, and the residue distilled, giving the *cyanide* as an oil, b. p. 145°/0·3 mm. (Found: C, 77·9; H, 7·2; N, 4·7. $C_{20}H_{23}O_2N$ requires C, 77·7; H, 7·4; N, 4·5%).

2-*Cyano*-2 : 2-*diphenylpropaldehyde* (VII).—The above acetal (3·4 g.) was hydrolysed by shaking it with 15% hydrochloric acid (13·5 ml.) in an atmosphere of nitrogen for 24 hours. The mixture was extracted with ether, the ethereal solution washed with a solution of potassium carbonate, and then with water, and dried (Na_2SO_4) and the ether distilled off. The residue distilled at 130—150°/0·6 mm. and became partly solid when kept overnight. After being pressed on porous plate and recrystallised from light petroleum (b. p. 60—80°), the *aldehyde* had m. p. 92—94° (yield 42%) (Found: C, 82·1; H, 5·7; N, 5·75. $C_{16}H_{13}ON$ requires C, 81·7; H, 5·5; N, 6·0%). The *azine* prepared from the aldehyde (2·85 g.) and 90% hydrazine hydrate (0·23 ml.) had m. p. 182—184° after recrystallisation from ethyl alcohol (Found: C, 82·1; H, 5·8; N, 12·2. $C_{32}H_{26}N_4$ requires C, 82·4; H, 5·6; N, 12·0%).

3-*Dimethylamino*-1 : 1-*diphenylbutyl Cyanide* (II; R = R′ = Me).—To the above aldehyde (5·0 g.) in ether (50 ml.) was added an ethereal solution of methylmagnesium iodide containing one molar equivalent, at 0° with stirring. A solid formed at once and stirring was continued for 30 minutes at room temperature. The Grignard complex was then decomposed with ammonium chloride solution, and the ethereal layer separated, washed with water, and dried (Na_2SO_4). After removal of the ether the residue was distilled in a high vacuum giving an oil at 154—156°/0·1 mm., which analysed correctly as the secondary *alcohol* (VIII) (Found: C, 81·0; H, 6·1; N, 5·6. $C_{17}H_{17}ON$ requires C, 81·25; H, 6·8; N, 5·6%).

To a mixture of the above compound (3·6 g.) and dimethylaniline (1·7 g.) in benzene (30 ml.) was added, with cooling and shaking, thionyl chloride (2·0 ml.) in benzene (10 ml.). The mixture was heated under reflux for 2 hours and then poured into ice-water, the benzene layer was separated, washed with water, and concentrated, and the residue distilled at 154°/0·2 mm., giving a product (2·0 g.) containing 10·2% of Cl (Calc. for $C_{17}H_{16}NCl$: Cl, 13·2%).

This crude chloro-compound (1·5 g.) was heated with 25% aqueous dimethylamine (10 ml.) for 6 hours at 130° in a sealed tube. On working up in the usual way, about 0·2 g. of basic material was obtained,

which gave a picrate, m. p. 148—149·5°, which showed no depression in m. p. when mixed with an authentic specimen of 3-dimethylamino-1 : 1-diphenylbutyl cyanide picrate of m. p. 149—150° (Found: C, 59·7; H, 5·6; N, 14·3. Calc. for $C_{28}H_{33}O_7N_5$: C, 59·2; H, 4·9; N, 13·8%).

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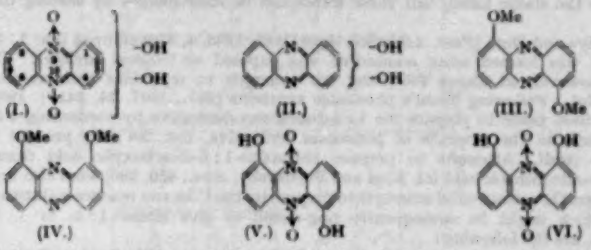
307. *The Phenazine Series. Part VIII. The Constitution of the Pigment of* Chromobacterium iodinum.

By G. R. CLEMO and A. F. DAGLISH.

It has been shown that the two hydroxyl groups in iodinin occupy the 1 : 5-positions. 1 : 2-, 1 : 5-, and 1 : 8-Dimethoxyphenazines have been synthesised, and the 1 : 5- and 1 : 8-isomers have been demethylated.

THE pigment of *Chromobacterium iodinum* was shown by Clemo and McIlwain (*J.*, 1938, 479) to be the di-*N*-oxide of a dihydroxyphenazine (I), and on catalytic reduction it gave a dihydroxydihydrophenazine which autoxidised to a dihydroxyphenazine (II).



Absorption spectra and certain qualitative tests showed that the bacterial pigment resembled alizarin but not quinizarin.

Of the ten possible dihydroxyphenazines, only the diacetyl derivatives of the 2 : 3- and the 2 : 6-isomers * had been previously described, and both differed from the derivative made from the pigment. Synthetic work towards the elucidation of the latter's constitution was interrupted in 1939, but the possibility that it was 1 : 2-dihydroxyphenazine was eliminated by Hegedüs (*Festschrift für E. C. Barell*, 1946), who synthesised this compound, the dimethyl ether, and the diacetate, and showed that they differed from the pigment analogues.

Independent syntheses of 1 : 2-dimethoxyphenazine were reported by Slack and Slack (*Nature*, 1947, **160**, 437) and Clemo and Daglish (*Nature*, 1947, **160**, 752): the melting point recorded in each case was 138—139°, whereas Hegedüs gave the melting point as 145°. In an attempt to clear up this anomaly, we sublimed a specimen of 1 : 2-dimethoxyphenazine, from Dr. Hegedüs to whom our best thanks are due, as well as a sample of our 1 : 2-dimethoxyphenazine, at 80—90° in a molecular still. The two sublimates still showed the original m. p.s, and the mixture melted at 138—144°; a crystallographic examination of the two samples has also failed to resolve this anomaly.

1 : 4-Dimethoxyphenazine was also described by Slack and Slack (*loc. cit.*). Instead of attempting the demethylation of this compound, we methylated the dihydroxyphenazine obtained from the pigment and obtained a compound, m. p. 245—246°, which differed from that prepared by Slack and Slack. Recently King, Clark, and Davis (*J.*, 1949, 3012) have described the demethylation of 1 : 4-dimethoxyphenazine using aluminium chloride in dry benzene.

The synthesis of 1 : 3-dihydroxyphenazine (Clemo and Daglish, *J.*, 1948, 2318) completed the investigation of the four possible isomers containing two hydroxy-groups in the same ring, and as it was also different from the dihydroxyphenazine obtained from iodinin, it became certain that in the natural product the two hydroxyl groups were in different benzene nuclei.

* The numbering shown in (I) is used in this paper solely to conform with that used in previous Parts of this series.

Attention was then directed to the preparation of 1 : 5- and 1 : 8-dimethoxyphenazine. Thus, 3-methoxy-*o*-benzoquinone and 2 : 3-diaminoanisole condensed together under the conditions used for 1-methoxyphenazine (*Org. Synth.*, 1946, **26**, 86) to give a mixture of 1 : 5- and 1 : 8-dimethoxyphenazines (III and IV) which were separated chromatographically on alumina. One of these compounds provided to be identical with the dimethoxyphenazine from iodinin, and both the isomers were smoothly demethylated by hydrobromic acid–acetic acid.

After many unsuccessful attempts to prepare either the 1 : 5- or 1 : 8-dimethoxyphenazine by an unambiguous synthesis, the 1 : 6-compound was eventually obtained by condensing 3-bromo-2-nitroanisole (Hodgson and Moore, *J.*, 1926, 155) and 3-nitro-2-aminoanisole (Blanksma, *Chem. Weekblad*, 1908, **5**, 789) to give 2 : 2′-dinitro-3 : 6′-dimethoxydiphenylamine. On reduction and ring closure of this amine under mild oxidising conditions (cf. Tomlinson, *J.*, 1939, 160, and Elderfield, Gensler, and Birstein, *J. Org. Chem.*, 1946, **2**, 817), the 1 : 5-dimethoxyphenazine was obtained; it was found to be identical to the dimethoxyphenazine derived from the pigment.

2 : 2′-Dinitro-3 : 6′-dimethoxydiphenylamine exists in three crystalline forms: a stable form (*A*), which forms prisms from alcohol or benzene, m. p. 118°; and two unstable forms (*B*) and (*C*), which crystallise from benzene–light petroleum (b. p. 60—80°) in yellow needles and red prisms, respectively. Both unstable forms melt at 104°, and when allowed to solidify change to the stable form. All three forms can be interchanged by seeding the solution in benzene.

Malaviya and Dutt (*Proc. Acad. Sci. Agra Oudh*, 1935, **4**, 319) claimed that 1 : 5-dimethoxyphenazine was formed when *o*-anisidine was exposed to tropical sunlight. Their product melted, however, at above 300°, and our attempts to reproduce their results have been unsuccessful. Following Wohl's phenazine synthesis (*Ber.*, 1901, **34**, 2446; 1903, **36**, 4135), attempts were made to prepare the 1 : 5-dimethoxy-derivative by condensing *o*-anisidine and *o*-nitroanisole in the presence of potassium hydroxide, but the only product isolated was phenazine itself. Attempts to prepare phenazine-1 : 5-dicarboxylic acid from anthranilic acid and *o*-nitrobenzoic acid (cf. Kögl and Postowsky, *Ann.*, **480**, 280) were also unsuccessful.

Amongst the unsuccessful attempts to prepare by the Ullmann reaction substituted diphenylamines which might be subsequently ring-closed to give either 1 : 5- or 1 : 8-dimethoxyphenazine, are the following:

(*a*) 3-Chloro-2-nitroanisole and 3-nitro-2-aminoanisole; (*b*) 2-chloro-3-nitroanisole and 3-nitro-2-aminoanisole; (*c*) 2-chloro-3-nitroanisole and 2-chloro-3-aminoanisole; (*d*) 3-chloro-2-nitroanisole and 3-chloro-2-aminoanisole; (*e*) 4-chloro-3 : 5-dinitrobenzoic acid and 4-chloro-3 : 5-bisacetamidobenzoic acid; (*f*) 4-chloro-3 : 5-dinitrobenzoic acid and 2 : 3-dinitroaniline.

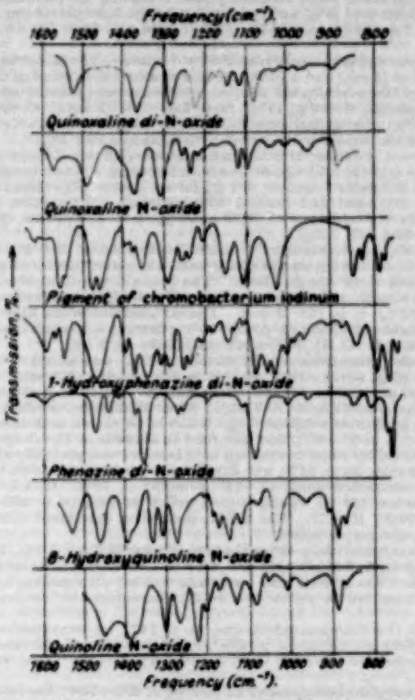
In an attempt to prepare 1 : 8-diaminophenazine, di-(2 : 6-dinitro-4-carbomethoxyphenyl)-amine was synthesised, but catalytic reduction gave an unstable blue hydrochloride which readily changed to a black polymeric product.

Although phenazine is only pale yellow, its di-*N*-oxide is deep orange. This is surprising in view of the absence of colour from most tertiary amine oxides, and the fact that azoxy-compounds are lighter in colour than the corresponding azo-derivatives. It is also surprising that the permanganate-coloured iodinin (V) is insoluble in water and gives an intense blue solution in alkali, whereas the yellow 1 : 5-dihydroxyanthraquinone which could have a similar bond structure gives only a red solution.

Pending a successful synthesis of either 1 : 5- or 1 : 8-dimethoxyphenazine it was considered, in view of the work of Flett (*J.*, 1948, 1441) which showed that infra-red absorption spectra differentiated between isomeric dihydroxyanthraquinones, that the same method might be expected to distinguish between 1 : 5- and 1 : 8-dihydroxyphenazines and their di-*N*-oxides. Thus, 1 : 8-dihydroxyphenazine di-*N*-oxide (VI) should show two N→O frequencies because the strengths of the two N→O bonds are unequal, a hydrogen bond being formed in only one case. However, in 1 : 5-dihydroxyphenazine di-*N*-oxide (V), both N→O groups interact with the adjacent hydroxyl group and only one N→O frequency should result.

The absorption spectra of iodinin, phenazine di-*N*-oxide and its 1-hydroxy-derivative, quinoline *N*-oxide and its 8-hydroxy-derivative, and quinoxaline *N*-oxide and di-*N*-oxide were kindly determined by Dr. Flett through the courtesy of Imperial Chemical Industries Limited, Dyestuffs Division. All aromatic nitro-compounds have an absorption band at 1350 cm.$^{-1}$, and this and another at 1075 cm.$^{-1}$ are shown by phenazine di-*N*-oxide. Quinoxaline di-*N*-oxide has a band at 1370 cm.$^{-1}$ and (possibly) the 1075 cm.$^{-1}$ band. In the mono-*N*-oxide the latter band is much weaker and is at 1100 cm.$^{-1}$, while the 1370 cm.$^{-1}$ band (including the small inflexion at longer wave-length) persists. It is very doubtful if either band is present in the

quinoline *N*-oxide spectrum (the 1390 cm.$^{-1}$ band may be present—note the inflexion), but both are probably shown by that of its 8-hydroxy-derivative (at 1395 cm.$^{-1}$—note the inflexion—and at 1040 cm.$^{-1}$). 1-Hydroxyphenazine di-*N*-oxide does not show either band clearly, and it is barely possible that iodinin shows them at 1290 cm.$^{-1}$ and 1020 cm.$^{-1}$, but in this case the characteristic inflexion of the shorter wave-length band is concealed by new bands. As a



diagnostic test for the presence of a 1-hydroxy-group in phenazine this method therefore fails. The complete change in character of the absorption spectrum of phenazine di-*N*-oxide on the introduction of a hydroxyl group indicates that a more profound electronic change has taken place than is evident from the formula (V) for the pigment.

Experimental.

(M. p.s are uncorrected. Microanalyses are by Mr. W. A. Campbell and Drs. Weiler and Strauss, Oxford.)

1-*Hydroxy*-2-*methoxy*-5 : 6 : 7 : 8-*tetrahydrophenazine*.—A solution of 5 : 6-dinitroguaiacol (0·5 g.) (Pollecoff and Robinson, *J.*, 1918, 648) in boiling alcohol (10 ml.) was mixed with concentrated hydrochloric acid (5 ml.) and excess of zinc dust (2 g.) was added. When the vigorous reaction had subsided, the solution was diluted with water, filtered, and a solution of *cyclo*hexane-1 : 2-dione (0·25 g.) in aqueous sodium hydrogen sulphite solution, containing sodium acetate (2 g.), was added. The mixture was boiled for five minutes, cooled, and filtered, yielding a red zinc complex which was suspended in chloroform and decomposed with hydrogen sulphide. The chloroform solution yielded the *tetrahydrophenazine* as orange-red prisms (0·1 g., 17%), m. p. 100° (Found : C, 67·7; H, 6·4; N, 12·7. $C_{12}H_{14}O_2N_2$ requires C, 67·8; H, 6·1; N, 12·2%).

1 : 2-*Dimethoxy*-5 : 6 : 7 : 8-*tetrahydrophenazine*.—A solution of 3 : 4-dinitroveratrole (11·7 g.) (Pollecoff and Robinson, *loc. cit.*) in boiling alcohol was reduced with zinc and hydrochloric acid, and then boiled with *cyclo*hexane-1 : 2-dione (5·6 g.) for two hours. The alcohol was removed, and the solution was basified with ammonium hydroxide and extracted continuously with ether. The tetrahydrophenazine was purified by extraction from ethereal solution with hydrochloric acid (3%), precipitation

with aqueous sodium hydroxide (5%), and re-extraction with ether. Removal of the solvent, followed by crystallisation from light petroleum (b. p. 40—60°), gave straw-coloured needles (6 g., 48%), m. p. 82—83° (King, Clark, and Davis, *loc. cit.*, give m. p. 82—83°) (Found: C, 69·0; H, 6·6; N, 11·9. Calc. for $C_{14}H_{12}O_2N_2$: C, 68·9; H, 6·6; N, 11·4%).

1 : 2-*Dimethoxyphenazine*.—The tetrahydro-compound (3 g.) and palladium–charcoal (0·9 g.; 10% palladium) were heated under reflux in *p*-cymene (30 ml.) for three hours. The cooled product was filtered and the solvent removed under reduced pressure, leaving the phenazine which was purified by extraction with hydrochloric acid (5%) and recrystallised from light petroleum (b. p. 80—100°), yielding orange-yellow blades (1·3 g., 44%), m. p. 138—139° (Found: C, 70·0; H, 5·4. Calc. for $C_{14}H_{12}O_2N_2$: C, 70·0; H, 5·0%).

Methylation of the Hydroxyphenazine prepared from Iodinin.—The dihydroxyphenazine (0·03 g.) was mixed with methyl alcohol (3 ml.) and a freshly prepared ethereal solution of diazomethane (0·166 g. in 10 ml.). After 48 hours the precipitated *dimethoxyphenazine* was filtered off and recrystallised from benzene yielding yellow needles (0·016 g., 47%), m. p. 245—246° (Found: C, 69·9; H, 4·4. $C_{14}H_{12}O_2N_2$ requires C, 70·0; H, 5·0%). A further amount, (making 56% in all) was obtained by removal of the solvent and extraction of the residue with sodium hydroxide solution (3%).

2 : 3-*Diaminoanisole*.—A solution of 2 : 3-dinitroanisole (2·5 g.) (Wrede and Strack, *Ber.*, 1929, **62**, 2053) in glacial acetic acid (50 ml.) was shaken with hydrogen at room temperature and atmospheric pressure in the presence of Adams's catalyst (0·1 g.) for six hours. The colourless solution was filtered, diluted with water (50 ml.), and just basified with ammonia. Extraction with ether (4 × 60 ml.) followed by distillation gave a colourless oil (1·22 g., 70%), b. p. 130°/5 mm. (Found: C, 60·9; H, 7·8. Calc. for $C_7H_{10}ON_2$: C, 60·9; H, 7·2%).

2-*Chloro*-3-*aminoanisole*.—A solution of 2-chloro-3-nitroanisole (5·4 g.) in aqueous acetic acid (54 ml., 50%) was stirred and heated on the steam-bath while iron powder (4 g.) was added during one hour; heating was continued for another hour. The product was diluted with hot water (100 ml.), basified with sodium carbonate, and steam-distilled. The distillate was extracted with ether, yielding a colourless oil (4·2 g., 93%), b. p. 125°/3 mm. The oil solidified when kept for several months, and was recrystallised from light petroleum (b. p. 40—60°), affording colourless needles of the *anisole*, m. p. 50° (Found: C, 53·6; H, 5·1. C_7H_8ONCl requires C, 53·3; H, 5·1%).

1 : 5- *and* 1 : 8-*Dimethoxyphenazine*.—Lead dioxide (27 g.) was added to a solution of pyrogallol 1-methyl ether (1·35 g.) (*Org. Synth.*, 1946, **26**, 90) in dry benzene (270 ml.). After being shaken for 20 minutes, the red solution was filtered and mixed with a solution of 2 : 3-diaminoanisole (1·03 g.) in benzene (26·8 ml.) and glacial acetic acid (10·7 ml.). After 90 minutes, the dark red solution was washed thoroughly with sodium hydroxide solution (5%), followed by water, and dried ($MgSO_4$), diluted with light petroleum (400 ml.; b. p. 60—80°), and adsorbed on alumina. The chromatogram was developed with benzene and a broad yellow band containing both isomers was gradually eluted. The first 150 ml. of eluent gave yellow needles, m. p. 247°, not depressed by admixture with the dimethoxyphenazine prepared from iodinin; extinction angle 42—44° (Found: C, 70·4; H, 4·7. Calc. for $C_{14}H_{12}O_2N_2$: C, 70·0; H, 5·0%). The last 150 ml. of eluent gave yellow needles, m. p. 253—254°, showing straight extinction (Found: C, 70·2; H, 4·7). The middle portion of the eluent contained a mixture of the two isomers, and was re-chromatographed.

1 : 5- *and* 1 : 8-*Dihydroxyphenazine*.—Dimethoxyphenazine (0·2 g.) (1 : 5-, 1 : 8-, or a mixture) was heated under reflux with hydrobromic acid (2·5 ml.; *d* 1·49) and glacial acetic acid (2·5 ml.) for 24 hours. The cooled product was diluted with water and treated with sodium hydroxide (5%) until the colour changed sharply from red to yellow (pH 4—5), whereupon a yellow precipitate formed and was removed and dried.

(*a*) The product from the dimethoxyphenazine, m. p. 247°, on recrystallisation from ethyl acetate yielded golden needles (0·02 g., 11%), m. p. 274°, not depressed by admixture with the dihydroxyphenazine prepared from iodinin (Found: C, 67·4; H, 3·9; N, 13·0. Calc. for $C_{12}H_8O_2N_2$: C, 67·9; H, 3·8; N, 13·2%).

(*b*) The *product* from the dimethoxyphenazine melting at 253—254° was recrystallised from benzene and gave orange-red plates (0·02 g., 11%), m. p. 295° (Found: C, 67·5; H, 3·9; N, 12·9%).

(*c*) The product obtained from the mixture of the two isomers was dissolved in benzene and adsorbed on alumina. The less strongly adsorbed, purple band contained the dihydroxyphenazine, m. p. 295°, and the more strongly adsorbed, red band contained the isomer, m. p. 274°.

2 : 2′-*Dinitro*-3 : 6′-*dimethoxydiphenylamine*.—3-Bromo-2-nitroanisole (0·78 g.) (Hodgson and Moore, *J.*, 1926, 155), 3-nitro-2-aminoanisole (0·565 g.), anhydrous potassium carbonate (0·67 g.), freshly reduced copper powder (0·1 g.), nitrobenzene (2 ml.), and a trace of water were stirred and heated at 220° for 2 hours (longer or shorter heating periods gave decreased yields). The cooled product was dissolved in boiling benzene (20 ml.) and filtered, light petroleum (30 ml.; b. p. 60—80°) added, and the mixture allowed to crystallise, affording a yellow solid which was recrystallised from alcohol yielding orange-red prisms of the *amine* (0·13 g., 12%), m. p. 118° (Found: C, 52·7; H, 4·2. $C_{14}H_{13}O_6N_3$ requires C, 52·7; H, 4·1%).

The same compound was obtained in 10% yield when the reagents were heated in the absence of solvent at 180° for 6 hours. The cooled product was extracted with ether; removal of the solvent gave a brown powder which was recrystallised from benzene–light petroleum (b. p. 60—80°), yielding either yellow needles, m. p. 104° (Found: C, 52·9; H, 4·1; N, 13·0. Calc. for $C_{14}H_{13}O_6N_3$: C, 52·7; H, 4·1; N, 13·2%), or red prisms, m. p. 104° (Found: C, 52·9; H, 4·0; N, 12·9%).

1 : 8-*Dimethoxyphenazine*.—A solution of 2 : 2′-dinitro-3 : 6′-dimethoxydiphenylamine (0·1 g.) in ethanol (8 ml.) was shaken with hydrogen at room temperature and atmospheric pressure for one hour in the presence of Adams's catalyst (0·05 g.). The colourless solution was filtered and acidified with concentrated hydrochloric acid (0·1 ml.), and the alcohol was removed, yielding a white hydrochloride; this was dissolved in water (5 ml.) and oxidised with a solution of ferric chloride (0·5 g.) in water (1 ml.). A dark red colour developed immediately, changing to brown with the formation of a yellow precipitate. After 12 hours, water (20 ml.) was added and the precipitated solid was recrystallised from benzene

yielding yellow needles (0·068 g., 90%), m. p. 247° not depressed by admixture with the *dimethoxyphenazine* prepared from iodinin (Found: C, 70·3; H, 5·2. $C_{14}H_{12}O_2N_2$ requires C, 70·0; H, 5·0%).

2 : 6-*Dinitro*-4 : 4'-*dicarboxydiphenylamine*.—A solution of 4-chloro-3 : 5-dinitrobenzoic acid (0·6 g.), *p*-aminobenzoic acid (4·8 g.), and sodium carbonate (2·6 g.) in water (340 ml.) was boiled for two hours. The cooled product was acidified and filtered, and the residue recrystallised from acetic acid, yielding orange prisms (12·8 g., 95%), m. p. 309° (Found: C, 47·2; H, 2·4. Calc. for $C_{14}H_9O_8N_3,C_2H_4O_2$: C, 47·2; H, 3·2%).

This compound (1·5 g.) was dried at 120° for three hours, added in small portions to a mixture of nitric acid (7·5 g.; *d* 1·5) and sulphuric acid (7·5 g.; *d* 1·825) and left for six hours, whereupon a crystalline precipitate of di-(2 : 4 : 6-trinitrophenyl)amine was formed; this was washed with water and recrystallised from acetic acid yielding yellow prisms (2·5 g., 75%), m. p. 241° (Found: C, 33·2; H, 1·1. Calc. for $C_{12}H_4O_{12}N_6$: C, 32·8; H, 1·1%).

2 : 6-*Dinitro*-4 : 4'-*dicarbomethoxydiphenylamine*.—A solution of the acid (5 g.) in methanol (80 ml.) containing sulphuric acid (4 ml.; *d* 1·825) was heated under reflux for two hours and cooled, and the solid filtered off. Recrystallisation from alcohol yielded yellow needles of the *ester* (5·9 g., 92%), m. p. 269° (Found: C, 51·3; H, 3·9. $C_{16}H_{11}O_{12}N_3$ requires C, 51·2; H, 3·5%).

Di-(**2 : 6-*dinitro*-4-*carbomethoxyphenyl*)*amine*.**—The dinitro-ester (3·6 g.) was added in small portions during one hour to nitric acid (18 ml.) (prepared by distilling nitric acid, *d* 1·5, with two volumes of sulphuric acid, *d* 1·825). After 24 hours, the mixture was poured on ice (500 g.) and filtered, and the residue crystallised from ethyl acetate, yielding yellow prisms of the *tetranitro*-compound (3·7 g., 78%), m. p. 246° (Found: C, 41·1; H, 2·5. $C_{15}H_{11}O_{19}N_6$ requires C, 41·3; H, 2·4%).

Wohl Reactions.—*o*-Nitroanisole (10 g.), *o*-aminoanisole (10 g.), and potassium hydroxide pellets (40 g.) were stirred and heated at 150° for 15 minutes. The product was diluted with water and steam-distilled. The solid residue was purified by extraction with acid, sublimed at 160° at 2 mm. pressure, and recrystallised from light petroleum (b. p. 40—60°), yielding phenazine (0·02 g., 0·2%), m. p. 172—173° not depressed by admixture with an authentic specimen (Found: C, 79·6; H, 4·5; N, 15·4. Calc. for $C_{12}H_8N_2$: C, 80·0; H, 4·4; N, 15·6%).

The same product was obtained by using powdered potassium hydroxide at 15—100°. The use of powdered zinc chloride at 180° (cf. Wohl and Lange, *Ber.*, 1910, **43**, 2186) gave no identifiable product.

Ultra-violet Irradiation of Amines.—Dilute solutions of *o*-anisidine in hydrochloric acid (0·5%) and anthranilic acid in water were exposed at a distance of six inches to an ultra-violet lamp for 24 hours. The dark brown solution was basified and extracted with benzene, and the extract adsorbed on a column of alumina. No trace of phenazine or substituted phenazine was found.

4-*Chloro*-3 : 5-*bisacetamidobenzoic Acid*.—4-Chloro-3 : 5-dinitrobenzoic acid (2 g.) was added during one hour to a solution of stannous chloride (11 g.) in hydrochloric acid (11·3 ml.; *d* 1·18), and the solution was stirred and heated on the steam-bath. Next morning the product was diluted with water, treated with hydrogen sulphide to remove tin, filtered and evaporated to dryness, yielding the crude *hydrochloride* (1·0 g.); this was heated under reflux for one hour with sodium acetate (0·8 g.) and acetic anhydride (0·8 g.) and poured into water, yielding white plates of the *bisacetamido*-compound (0·8 g., 36·5%), m. p. 187—188° (Found: C, 45·6; H, 4·5. $C_{11}H_{11}O_4N_2Cl$ requires C, 48·8; H, 4·1%).

3-*Chloro*-2-*benzamidophenol*.—3-Chloro-2-nitrophenyl benzoate (6 g.) was added during one hour to a stirred suspension of iron filings (13·4 g.) in aqueous acetic acid (14·5 ml.; 5%) on the steam-bath. The product was liberated with sodium carbonate, filtered off, and extracted with boiling alcohol, yielding white plates of the *benzamido*-compound (2·0 g., 56·1%), m. p. 155° (Found: C, 62·7; H, 4·4. $C_{13}H_{10}O_2NCl$ requires C, 63·0; H, 4·0%). The product showed the normal reactions of a phenol and an amide, indicating the migration of the benzoyl group during the reduction.

Our renewed thanks are due to Professor Dunlop (Bacteriology Department) for growing the further batches of pigment needed to finish this research. One of us (A. F. D.) is indebted to the Ministry of Education and Durham County Education Committee for maintenance grants, and to the authorities of King's College, Newcastle-on-Tyne, for the award of a Postgraduate Studentship.

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Newcastle-on-Tyne, 1.

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308. *Quinamine. Part V.* epi*Quinamine and* epi*Cinchonamine.*

By C. C. J. Culvenor, L. J. Goldsworthy, K. S. Kirby, and Sir Robert Robinson.

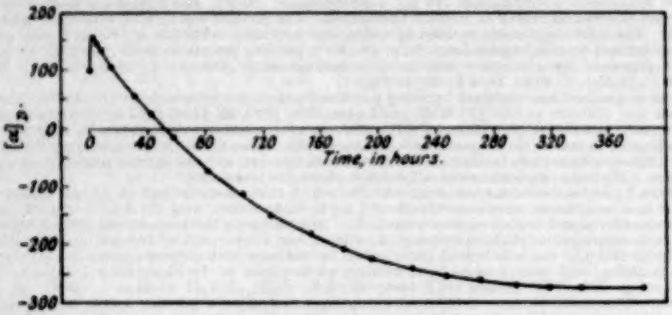
When heated with alcoholic potassium hydroxide, quinamine undergoes rapid epimerisation with formation of about 50% of *epi*quinamine. A slower conversion into *iso*quinamine and *epi*-*iso*quinamine proceeds simultaneously, so that a true equilibrium is not attained. *epi*Quinamine is probably identical with conquinamine, a minor *Cinchona* alkaloid which is a congener of quinamine. *epi*Quinamine is reduced by lithium aluminium hydride to *epi*-cinchonamine, a stereoisomeride of cinchonamine which has not been isolated from natural sources. Supporting evidence has been obtained for the formulation of the *iso*quinamines as the indoxyl derivatives (V). The structure (VI) for *apo*quinamine is confirmed by reduction of this base to a mixture of cinchonamine and *epi*cinchonamine. It is considered that the epimerisation of quinamine occurs at $C_{(3)}$ in the quinuclidine nucleus.

The conversion of quinamine into *iso*quinamine by heating it with amyl-alcoholic potassium hydroxide was reported in Part III (*J.*, 1949, 735), and it was stated that a second isomer was

probably also formed since, under similar conditions, dihydroquinamine gave rise to two isomeric dihydro*iso*quinamines (provisionally termed -I and -II). A more detailed investigation has now been made of the action of alcoholic alkali on quinamine, and it is found that, in addition to *iso*quinamine, two other isomerides, *epi*quinamine and *iso*quinamine-II, are produced together with some unidentified material. Under the conditions given in Part III for the preparation of *iso*quinamine, all three products are formed and may be isolated by a suitable procedure. *iso*Quinamine is the main product (48%), while *epi*quinamine is obtained in very small amount along with a little unchanged quinamine.

*iso*Quinamine-II is apparently a diastereoisomeride of *iso*quinamine: the ultra-violet absorption spectra of the two substances are very similar (Fig. 3, where the II-isomer is recorded as *epi-iso*quinamine) and both substances are yellow and exhibit the same green fluorescence in alcoholic solution. However, *iso*quinamine-II resembles dihydro*iso*quinamine-II in that the solid crystals show a blue fluorescence in ultra-violet light, in contrast to the bright yellow fluorescence of solid *iso*- and dihydro*iso*-quinamine-I. In harmony with this conclusion *iso*quinamine-II is converted quantitatively into dihydro*iso*quinamine-II on hydrogenation in the presence of palladised charcoal.

FIG. 1.



Change in optical rotation on heating quinamine (75 mg.) with a solution of sodium (80 mg.) in alcohol (12 c.c.) in a sealed tube at 80°.

When quinamine is heated with ethyl-alcoholic potassium hydroxide, there is a rapid increase in the optical rotation of the mixture, and after 2½ hours *epi*quinamine may be isolated in about 40% yield, the remaining quinamine being mostly recovered unchanged. The yield of *epi*quinamine is not increased, but rather decreased, by a longer period of heating, the actual change in optical rotation with time of heating (with alcoholic sodium ethoxide at 80°) being as shown in Fig. 1. The rotation rises rapidly to +156° (corresponding to 53% of *epi*quinamine) and then falls until it reaches a final steady value of −275° after 320 hours. After this prolonged heating, the only isolable products are *iso*quinamine-I ($[\alpha]_D$ −424°) and *iso*quinamine-II ($[\alpha]_D$ −269°), the latter in somewhat the smaller amount. The proportions of these products were not even approximately those which might be inferred from the final value of the optical rotation, so that unidentified by-products must also have been formed.

*epi*Quinamine may be partly reconverted into quinamine by a similar heating with ethyl-alcoholic potassium hydroxide for 2½ hours. The yield of quinamine was 30% and the unchanged *epi*quinamine was recovered. It is apparent therefore, that alcoholic alkali induces a rapid reversible reaction, quinamine $\rightleftharpoons$ *epi*quinamine, which does not reach a true equilibrium because of the slow irreversible transformation of one or both compounds into the *iso*quinamines and other substances.

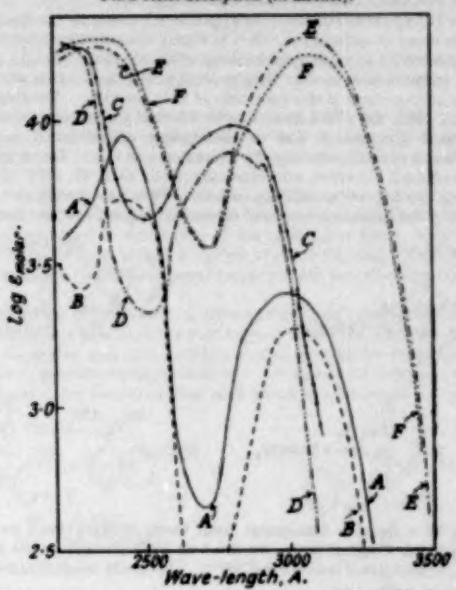
*epi*Quinamine has an ultra-violet absorption spectrum which is very similar to that of quinamine (Fig. 2), while its infra-red absorption spectrum confirms the absence of a carbonyl group. It may be converted into *apo*quinamine and quinamicine by the methods used for quinamine (Part I., *J.*, 1945, 524).

Although confirmation by direct comparison has not been possible, it is almost certain that *epi*quinamine is identical with the alkaloid conquinamine, $C_{19}H_{24}O_2N_2$, m. p. 123°, $[\alpha]_D$ +203°, which accompanies quinamine in small relative amount in *Cinchona* bark and was first isolated

by Hesse (*Ber.*, 1877, **10**, 2158). Conquinamine is reported to form a sparingly soluble nitrate (Oudemann, *Annalen*, 1879, **197**, 48) and possession of the same property by *epi*quinamine provides the basis for its ready separation from quinamine. Unfortunately, although a number of salts of conquinamine have been prepared, no melting points are recorded, and further comparison in this way is not possible. Conquinamine may also be converted into *apo*quinamine and quinamicine (Hesse, *Annalen*, 1881, **209**, 64, 67).

FIG. 2.

Ultra-violet absorption (in alcohol).



(*A*) *Quinamine.*
(*B*) *epiQuinamine.*
(*C*) *Cinchonamine.*
(*D*) epi*Cinchonamine.*
(*E*) apo*Quinamine.*
(*F*) *Acetyl*apo*quinamine.*

Further evidence of the nature of *epi*quinamine is provided by the fact that, like quinamine, it may be reduced by means of lithium aluminium hydride. Goutarel, Janot, Prelog, and Taylor (*Helv. Chim. Acta*, 1950, **33**, 150) have shown that quinamine is reduced by this reagent to cinchonamine, the net result being the loss of one oxygen atom. On repeating this experiment we have obtained the intermediate dihydro-derivative, mixed possibly with some unchanged quinamine, and subsequently dehydrated it to cinchonamine by heat. *epi*Quinamine is reduced in a similar manner to an isomeride of cinchonamine which exhibited a similar ultra-violet absorption spectrum (Fig. 2) and is termed *epi*cinchonamine. It was found in this case that the dihydro-derivative underwent spontaneous dehydration in solution in ether at the ordinary temperature. From these observations it is clear that *epi*quinamine is a diastereoisomeride of quinamine.

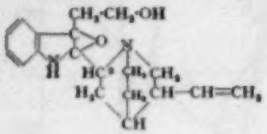
On the basis of the formula (II) proposed by Prelog and his collaborators (*loc. cit.*) for cinchonamine it is clear that stereoisomeric differences must be concerned with the circumstances obtaining in the quinuclidine nucleus, and cannot involve the indole moiety of the molecule. And further, since the isomerism of quinamine and *epi*quinamine persists in cinchonamine and *epi*cinchonamine, we may conclude that the original epimerisation of quinamine occurs in the quinuclidine nucleus. The existence of two *iso*quinamines and dihydro*iso*quinamines is obviously to be attributed to the same cause as that of two quinamines and two cinchonamines.

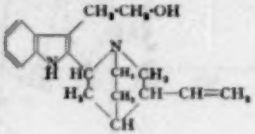
Hence we propose to adopt one system of nomenclature in the three cases and to replace the names *iso*quinamine-II and dihydro*iso*quinamine-II by *epi-iso*quinamine and dihydro*epi-iso*quinamine, respectively.

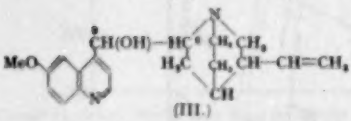
Further evidence for the diastereoisomeric nature of cinchonamine and *epi*cinchonamine has been provided by the formation of both bases when *epi*quinamine was reduced with sodium and alcohol (see below).

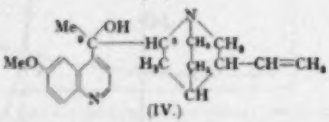
This observation identifies the asymmetric carbon atom concerned in the epimerisation as $C_{(9)}$ in the quinuclidine ring, a deduction in harmony with *a priori* consideration based on our existing knowledge of racemisation phenomena in this group.

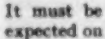
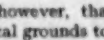
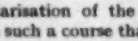
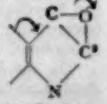
The occurrence of the epimerisation has an important bearing on the question of the function of the second oxygen atom in quinamine, for it is found that neither cinchonamine (II) nor the *iso*quinamines are affected by prolonged heating with alcoholic alkali. This precludes the possibility that the racemisation is due simply to the hydrogen atom attached to $C_{(9)}$ being sufficiently labile *per se* to permit of the inversion at that position. Doering, Cortes, and Knox (*J. Amer. Chem. Soc.*, **1947**, **69**, 1700) have concluded that the racemisation at $C_{(8)}$ in quinine, cinchonine, and related alkaloids is due to preliminary oxidation of (say) quinine (III) to quininone and enolisation of this to destroy the asymmetry at $C_{(8)}$. This is further substantiated by the finding of Woodward, Wendler, and Brutschy (*ibid.*, **1945**, **67**, 1427) that methylquinidine (IV) is unaffected by heating with alcoholic alkali. This base bears the hydroxyl group at $C_{(9)}$ but the potentiality for oxidation and enol formation is precluded by the methyl group.

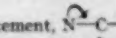

(I.)


(II.)


(III.)


(IV.)

Without arriving at a definite conclusion from these striking facts as to the validity of Doering's hypothesis in its simplest form, we must at least recognise that racemisation at $C_{(8)}$ will occur if $C_{(9)}$ is $-CO-$ and not if it is $-CMe(OH)-$. This could be attributed to the potentiality for the displacement in the former case, or some analogous condition of $-CH(OH)-$ which is not possible with $-CMe(OH)-$. It could, for example, be . In any case the essential feature is a positive charge, not necessarily a full one, on $C_{(9)}$. With the ethylene oxide formula for quinamine the same potentiality exists through the displacement . It must be noted, however, that polarisation of the epoxide group in (I) would not be expected on theoretical grounds to take such a course that $C_{(9)}$ would acquire a positive charge. The general effect of the nitrogen atom should favour the other direction of polarisation.  promotes  rather than  . An effect of the benzene nucleus, if present at all, should be in the same sense, as shown in the expression 

More plausibly an electromeric displacement,  , may be postulated (and this affords an explanation of the very weak basic strength of the hydroindole-nitrogen atom) but this process does not provide $C_{(9)}$ with a positive charge.

At this stage we are not compelled to invoke a special hypothesis of polarisation, for it may

well be that the inductive effect of N and O combined with the distortion of valency-electronic configuration in the three-membered ring bares the nucleus of C_{10}, inducing an electric field sufficient to loosen a proton on a neighbouring carbon atom. A decision on these points must await study of appropriate models, which are not available at the present time. The evidence in favour of the formulation of quinamine as an epoxide (I) is all indirect. It may be summarised as follows.*

(*a*) Of the two oxygen atoms, one has aliphatic hydroxy-function and the other must have ether function (absence of CO bond in the infra-red spectrum, absence of *N*-oxide group).

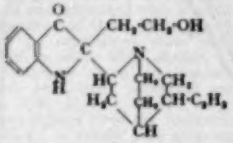
(*b*) This ethereal oxygen is the site of reduction ($LiAlH_4$) and the product is a tertiary alcohol (not an aromatic indole derivative) which easily loses the elements of water with formation of an indole derivative.

(*c*) There is independent evidence that *iso*quinamine is a 2 : 2-disubstituted indoxyl (cf. Part IV and below), and the rearrangement of (I) required to produce such a substance (V) is of a normal type.

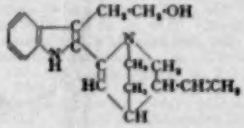
Consideration of (*a*), (*b*), and (*c*) leads to the conclusion that an epoxide constitution provides the best explanation of the findings; (*b*) indicates that the epoxide oxygen is attached to the α- or the β-position of the indole nucleus, and (*c*) indicates that it is attached to both these positions.

The stability of quinamine towards thiourea, potassium selenocyanate, or potassium ethyl xanthate, which react very readily with simple ethylene oxides (Davies *et al.*, *J.*, 1946, 1050; 1949, 278), may be explained as the result of the protective effect of the heavy substituents. All these anionoid reagents must attack a carbon atom of the ring. Cationoid reagents, such as acids, may however attack the more exposed oxygen atom and they do in fact react readily with quinamine.

After the identification of the true 2 : 2-tetramethyleneindoxyl (Plant and Robinson, *Nature* 1950, **165**, 36) a model was available for this type of structure, and the similarity in properties between the *iso*quinamines and this substance was seen to be even more striking than the resemblance to the 4-ketotetrahydroquinolines. Independent evidence now strongly favours the indoxyl constitution for *iso*quinamines and hence the structure (V) in relation to Prelog's suggestions.



(V.)



(VI.)

The *m*-dinitrobenzene test for the group $\begin{matrix} C \\ C \end{matrix}\!>\!CH\cdot CO\cdot$ has been improved and found to give a positive reaction with phenyl *iso*propyl ketone, 4-ketotetrahydroquinoline, and hexahydroacridone. It is entirely negative with 2 : 2-tetramethyleneindoxyl and with the *iso*quinamines and dihydro*iso*quinamines.

Furthermore Elderfield and Maggiolo (*J. Amer. Chem. Soc.*, 1949, **71**, 1906) have shown that 4-ketotetrahydroquinolines can be dehydrogenated to 4-hydroxyquinolines by means of palladium catalysts and maleic acid. We have acquainted ourselves with the proper conditions and find that the *iso*quinamines cannot be dehydrogenated in a similar manner.

The structure (V) suggests no plausible mechanism for epimerisation at C_{10}, and we have been unable to bring about any transformation of *iso*quinamine into *epi-iso*quinamine, or *vice versa*, in the presence of boiling alcoholic sodium ethoxide. It is highly probable that quinamine and *epi*quinamine correspond to *iso*quinamine and *epi-iso*quinamine, although not necessarily respectively. No direct proof of these relations could be obtained because of the rapid equilibrium established between quinamine and *epi*quinamine, much more rapid than the conversion of either into *iso*quinamine.

Fig. 3 shows the ultra-violet absorption spectrum of *iso*quinamine compared with those of

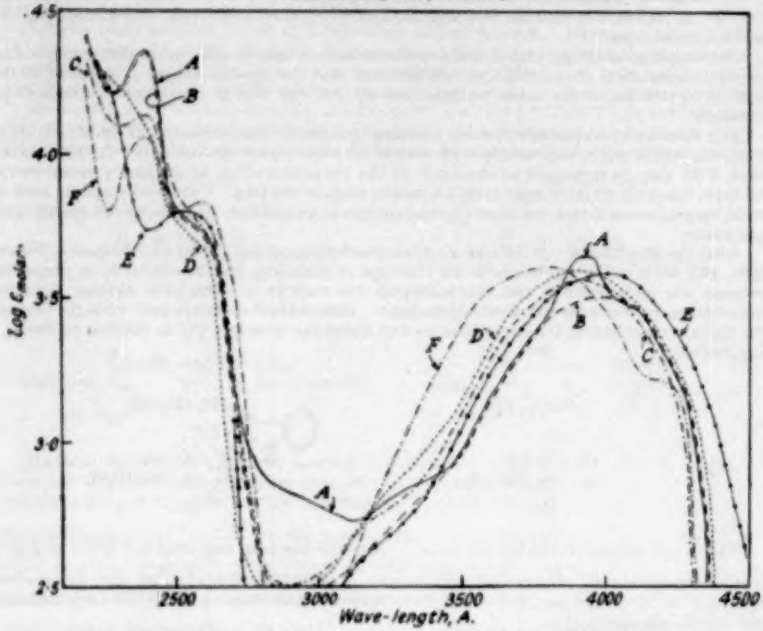
* *Added in Proof.*—Withop (private communication) has suggested an alternative formulation of quinamine in which the free hydroxyl is in position 3 of the indole nucleus, the oxide ring being 5-membered. This recalls the relation of scopine to oscine, and the new formula appears to us to be preferable to the ethylene oxide structure. The points made in the text are still relevant.

model substances. It can be seen that the results are in harmony with the substituted indoxyl theory but cannot be said to exclude a hydroquinolone hypothesis.

The ultra-violet absorption spectra of *apo*quinamine and acetyl*apo*quinamine are shown in Fig. 2. The indications are that the indole nucleus is present with an additional conjugated centre, and formula (VI) accords with these results. In confirmation it has been found that reduction of *apo*quinamine with sodium and alcohol affords a mixture of cinchonamine and *epi*cinchonamine. The formula (VI) also explains the weak basicity of *apo*quinamine (cf. Hesse, *Ber.*, 1872, **5**, 265) which is exemplified by its extraction from a solution in dilute acetic acid with ether (the purification procedure specified in Part I should therefore be modified). The

FIG. 3.

Ultra-violet absorption (in alcohol).



(*A*) iso*Quinamine*. (*D*) *Dihydro*epi-iso*quinamine*.
(*B*) *Dihydro*iso*quinamine*. (*E*) 2 : 2-*Tetramethyleneindoxyl*.
(*C*) epi-iso*Quinamine*. (*F*) 4-*Ketotetrahydroquinoline*.

constitution of *apo*quinamine is similar to that of *neo*strychnine in that both bases are vinylamine derivatives. Coupling of *neo*strychnine with *p*-nitrobenzenediazonium salts in weakly acid solution causes oxidative fission of the double bond and formation of a *p*-nitrophenylhydrazone:

$$CH{:}CH\text{-}N\text{-} \longrightarrow CN\text{-}NH\text{-}C_6H_4\text{-}NO_2 + OCH\text{-}N\text{-}$$

The product gives at once a light cherry-red colour in alcoholic sodium hydroxide solution.

In the case of *apo*quinamine an orange-coloured amorphous substance was precipitated and this was insoluble in N-hydrochloric acid. Its orange-yellow solution in alcohol became only pale greenish-brown on the addition of sodium hydroxide but this solution developed an intense bluish-red (damson) colour in a few seconds. It is clear that, if the coupling reaction is analogous to that of *neo*strychnine, the last stage is completed by the action of alkali. On acidification, the bluish-red solution became orange-yellow and the bluish-red colour was at once restored by the addition of sodium hydroxide.

Experimental.

Action of Amyl-alcoholic Potassium Hydroxide on Quinamine.—A solution of quinamine (4 g.) and potassium hydroxide (0·72 g.) in amyl alcohol (the technical mixture, chiefly *iso*amyl alcohol) (50 c.c.) was refluxed for 45 minutes, the amyl alcohol removed by steam-distillation, and the residual resin separated and dissolved in a little hot ethyl alcohol. On cooling, bright yellow prisms of *iso*quinamine (1·62 g.), m. p. 203—205°, were obtained and concentration of the filtrate, after the addition of a little water, gave pale yellow clustered needles of (crude) quinamine (0·19 g.), m. p. 165—169°, mixed m. p. 170—174°. After further concentration yellowish-green needles of *iso*quinamine (0·12 g.) separated, having m. p. 201—203° and mixed m. p. 203—204°. The mother-liquors were evaporated *in vacuo* and extracted with benzene, and the washed and dried extract was passed through an alumina column. A rapidly moving band, colourless in ordinary light but showing white fluorescence in ultra-violet light, was collected first and, on evaporation gave a colourless oil which slowly solidified. Recrystallisation from light petroleum afforded material from which quinamine (0·01 g.; hard knobs of needles), m. p. 169—172°, mixed m. p. 171—173°, and *epiquinamine* (0·16 g., large prisms), m. p. 110—113°, were easily separated by hand-picking; the residual solid (0·03 g.) was clearly a mixture of these two components only. Elution of the remaining complex band system with benzene containing 5% of methanol gave the principal components as a yellow band exhibiting chiefly yellow fluorescence in ultra-violet light. However, the band was not homogeneous and both the fore and rear sections showed that a white-fluorescent substance was also present. A second absorption on alumina did not effect a separation, so the solution was evaporated (total solid : 0·62 g., m. p. 145—165°) and the residue recrystallised from benzene with very slow cooling of the solution. In this way, the larger part of the material separated as large, yellowish-green prisms (0·3 g.; m. p. 181—183°) which showed a bluish-white fluorescence in ultra-violet light and were readily separated by hand-picking from smaller, bright yellow prisms of *iso*quinamine (m. p. 195—199°, mixed m. p. 197—201°) which has a bright yellow fluorescence. The yellowish-green prisms were recrystallised from benzene, to give *epi-iso-quinamine*, m. p. 182·5—183·5°, $[\alpha]_D^{18}$ −269° ± 5° (*c*, 1·3 in alcohol) (Found : C, 72·5; H, 7·5; N, 9·2. $C_{19}H_{24}O_2N_2$ requires C, 73·0; H, 7·7; N, 9·0%). A mixture with quinamine melted at 152—158°. The aqueous layer in the steam-distillation flask from which the original reaction product was centrifuged was concentrated to a small volume and extracted with chloroform, affording a solid consisting almost entirely of *iso*quinamine (0·14 g.), m. p. 199—201°, mixed m. p. 200—202° (total yield of *iso*quinamine, 1·90 g., 48%).

*Hydrogenation of epi-iso*Quinamine.—*epi-iso*Quinamine (50 mg.) and palladised charcoal (15 mg.) were shaken in alcohol with hydrogen at the room temperature and pressure for 3 hours. The filtered and concentrated solution furnished dihydro*epi-iso*quinamine (50 mg.), m. p. 193—196°, mixed m. p. 197—200°.

Action of Ethyl-alcoholic Potassium Hydroxide on Quinamine.—A solution of quinamine (1·0 g.) and potassium hydroxide (0·2 g.) in ethyl alcohol (12 c.c.) was refluxed for 2 hours, the alcohol was removed *in vacuo*, water was added, and the products were extracted with ether. The solid left on evaporation of the extract was triturated with *N*-nitric acid (5 c.c.) and water (6 c.c.), and the mixture filtered after 2 hours. Basification of the filtrate gave unchanged quinamine (0·56 g.), m. p. 164—168°. The solid nitrate (0·45 g.) crystallised from water in stout prisms (0·38 g.), m. p. 202° (decomp.), which were dissolved in warm 60% alcohol. The solution was neutralised with ammonia and allowed to cool. *epi*Quinamine (0·25 g.) separated as long, prismatic needles, m. p. 119—121°. Recrystallisation from light petroleum gave prisms, m. p. 120—121°, $[\alpha]_D$ +197° (*c*, 2·5 in alcohol) (Found : C, 72·9; H, 8·0; N, 9·0. $C_{19}H_{24}O_2N_2$ requires C, 73·0; H, 7·7; N, 9·0%). Neutralisation of the mother-liquors from the recrystallisation of the crude *epi*quinamine nitrate yielded a further amount (0·03 g.) of nearly pure *epi*quinamine, m. p. 110—112°, so that in subsequent preparations, recrystallisation of the nitrate could be eliminated.

The change in optical rotation of the reaction mixture was followed by heating at 80° a solution of quinamine (75 mg.) and sodium (50 mg.) in absolute alcohol (9·45 g.) in a special sealed tube which functioned also as a polarimeter tube. This was a Pyrex tube, approx. 1 cm. × 10 cm., with optically flat plates sealed on each end, and a side-arm in the middle for filling and sealing. The alcohol used was purified by refluxing it with zinc and sodium hydroxide and distilling it from sodium, and the filling of the tube performed as far as possible under nitrogen in order to minimise colouring of the solution (cf. Doering, Cortes, and Knox, *J. Amer. Chem. Soc., loc. cit.*). With these precautions, the optical rotation could be easily determined even after heating for 350 hours, although the final products were themselves yellow. The results are shown in Fig. 1. After the experiment, the solution was concentrated, a little water added, and the product allowed to crystallise. Clusters of yellow needles were obtained which showed partly yellow and partly white fluorescence in ultra-violet light. Hand-picking gave *iso*quinamine (yellow prisms), m. p. 195—198°, mixed m. p. 197—201°, and *epi-iso*-quinamine (needles), m. p. 156—166°, mixed m. p. 169—178°. The mother-liquors, on further dilution with water, gave *epi-iso*quinamine as a white-fluorescent solid, crystallising from benzene in yellow needles, m. p. and mixed m. p. 182—183°.

Conversion of epi*Quinamine into Quinamine.*—*epi*Quinamine (50 mg.), potassium hydroxide (0·1 g.), and ethyl alcohol (3 c.c.) were refluxed for 2 hours, and the product was converted into the nitrates in the manner described above. *epi*Quinamine nitrate (26 mg.), m. p. 197°, was separated, and neutralisation of the filtrate gave a solid (16 mg.), m. p. 150—156°, which was essentially quinamine. On recrystallisation from aqueous alcohol, it formed glistening needles, m. p. 167—169°, mixed m. p. 169—173°.

Dehydrogenation of 4-Ketotetrahydroquinoline.—Water (2 c.c.) to which 4-ketotetrahydroquinoline (50 mg.) and palladised charcoal (10 mg.; 10% Pd) had been added was refluxed for 14 hours, and then filtered and evaporated. The residue was washed with ether and crystallised from dioxan to give 4-hydroxyquinoline (30 mg.), m. p. and mixed m. p. 195—197°. When the experiment was carried out with the addition of maleic acid as prescribed by Elderfield and Maggiolo (*loc. cit.*) in similar cases the

product separated as clusters of pale yellow needles, m. p. 227°, from hot water, and was apparently formed by combination of two molecules of 4-hydroxyquinoline with one molecule of maleic acid (Found: C, 65·6; H, 4·7; N, 6·9. $C_{26}H_{18}O_4N_2$ requires C, 65·0; H, 4·4; N, 6·9%). This substance was not formed by refluxing a mixture of 4-ketotetrahydroquinoline, maleic acid, and water without a catalyst. The maleic acid was transformed into fumaric acid.

Conversion of epi*Quinamine into* apo*Quinamine.*—*epi*Quinamine (50 mg.) was heated with an excess of acetyl chloride in refluxing benzene for 4 hours, the solvent evaporated, and the residue dissolved in a little alcohol and refluxed for 1 hour with potassium hydroxide (0·2 g.) in aqueous alcohol. The alcohol was removed *in vacuo* and the product, isolated by means of ether, taken up in dilute acetic acid, and the solution clarified centrifugally. Addition of an aqueous solution of potassium iodide (0·15 g.) precipitated an oil which slowly solidified. After 2 hours at 0°, crude *apo*quinamine hydriodide (60 mg.), m. p. 180—185°, mixed m. p. 186—190°, was collected. Neutralisation of a warm, aqueous-alcoholic solution of the hydriodide gave white prisms of *apo*quinamine, m. p. 110—111°, mixed m. p. 110—112°.

Conversion of epi*Quinamine into Quinamicine.*—A solution of *epi*quinamine (50 mg.) in 10% acetic acid (0·5 c.c.) was refluxed for 48 hours and the base precipitated with ammonia. The gum was washed by decantation, taken up in dilute acetic acid, and mixed with alcoholic picric acid. The picrate, which formed, crystallised from water in very small yellow needles, m. p. and mixed m. p. 195—196° (decomp.).

Reduction of Quinamine with Lithium Aluminium Hydride.—A solution of lithium aluminium hydride (0·04 g.) in ether (2 c.c.) was gradually added to one of quinamine (0·1 g. in 10 c.c.), and the mixture was refluxed for 15 minutes. Water was added to decompose the excess of hydride, and the washed and dried ethereal solution was evaporated at room temperature to give a colourless amorphous solid. The composition of this substance, and its subsequent conversion by heat into cinchonamine, indicated that it was the *dihydro*-derivative, formed by the reductive fission of the epoxide ring, mixed possibly with some unchanged quinamine. When heated it began to soften at 60°, then gradually melted with evolution of gas, partly resolidified at about 100°, and slowly melted again as the temperature rose to 150° (Found, in material dried *in vacuo* at the ordinary temperature: C, 72·4; H, 9·0. $C_{19}H_{24}O_2N_2$ requires C, 72·5; H, 8·3%). Dehydration of this compound by heating it at 12 mm. for 1 hour at 150°, and finally for 10 minutes at 190°, followed by crystallisation from benzene–light petroleum, yielded cinchonamine, identified by m. p. and mixed m. p. 184° with an authentic specimen.

epi*Cinchonamine.*—Reduction of *epi*quinamine with lithium aluminium hydride, under precisely the conditions described above for the reduction of quinamine, yielded a colourless solid, very similar in composition and behaviour on heating to the product that was obtained from quinamine (Found, in material dried *in vacuo* at the ordinary temperature: C, 72·2; H, 8·4; N, 8·2. $C_{19}H_{24}O_2N_2$ requires C, 72·5; H, 8·3; N, 8·9%). Considerable difficulty was being experienced in attempts to obtain from this amorphous substance either cinchonamine, or an isomer thereof, by high-temperature dehydration when a chance observation led to the discovery that dehydration could occur spontaneously at the ordinary temperature. It was noticed that some crystals had separated from a concentrated ethereal solution of the reduction product, which had been kept for about an hour at room temperature. These proved to consist of the isomer of cinchonamine which we have designated epi*cinchonamine*. The following procedure was then adopted for its preparation: A solution of lithium aluminium hydride (0·7 g.) in ether (28 c.c.) was gradually added to one of *epi*quinamine (1·43 g. in 30 c.c.), and the solution was refluxed for 3 hours. The excess of hydride was decomposed by the cautious addition of water, and the ethereal solution was washed, dried, and concentrated to a volume of approx. 10 c.c. When the solution was kept, crystals of pure *epi*cinchonamine separated in the form of long prisms (0·36 g.), m. p. 168°, $[\alpha]_D$ +48° (*c*, 2·0 in alcohol) (Found: C, 76·9; H, 8·1; N, 9·2. $C_{19}H_{24}ON_2$ requires C, 77·0; H, 8·1; N, 9·5%). By submitting the mother-liquor from the crystallisation to further treatment with lithium aluminium hydride an additional small amount (0·12 g.) of pure *epi*cinchonamine was obtained.

*epi*Cinchonamine closely resembles cinchonamine in crystalline form and solubility in the common solvents. It is readily soluble in alcohol, chloroform, or benzene, less so in ether, very sparingly so in light petroleum, and it is almost insoluble in water. Like cinchonamine it forms a very sparingly soluble *nitrate*, which separates as oily droplets, soon becoming crystalline, on adding an aqueous solution of potassium nitrate to one of the hydrochloride. The salt, recrystallised from hot water, in which it is moderately readily soluble, has m. p. 197° (Found: C, 63·5; H, 7·0. $C_{19}H_{24}ON_2,HNO_3$ requires C, 63·5; H, 7·0%). The behaviour of *epi*cinchonamine towards Ehrlich's reagent is the same as that of cinchonamine. No coloration is given in the cold, but on heating a red colour develops, which is intensified to purple by the addition of a trace of sodium nitrite. When *epi*cinchonamine is treated with a methyl-alcoholic solution of vanillin, with the addition of concentrated hydrochloric acid, a rose colour develops at once in the cold and slowly intensifies to a reddish purple. When the solution is heated, the colour is almost discharged, changing to a faint yellow, which turns to red on the addition of a trace of sodium nitrite. Cinchonamine, when treated in the same way under exactly comparable conditions, behaves differently. On mixing the reagents no colour is given in the cold, but on heating a faint rose colour develops which intensifies to red on the addition of a trace of nitrite.

Attempts to Epimerise Cinchonamine.—No change in the optical rotation of a solution of cinchonamine (0·1 g.) in ethyl alcohol (14 c.c.) containing potassium hydroxide (0·02 g.) was observed after heating in a sealed tube at 70° for 12 hours. Heating with more concentrated alkali at a higher temperature and for a longer period similarly had no effect; there was no change in rotation when a solution of the alkaloid (0·05 g.) in amyl alcohol (5 c.c.) containing potassium hydroxide (0·1 g.) was heated for 2 days at 120°.

Reduction of apo*Quinamine.*—A refluxing solution of *apo*quinamine (0·2 g.) in dry ethyl alcohol (10 c.c.) was treated with small pieces of sodium (0·5 g.). When all the sodium had dissolved, water (10 c.c.) was added and the alcohol removed *in vacuo*. The product separated first as an emulsion but crystallised before all the alcohol had been removed; after some time at 0°, white needles (0·2 g.), m. p. 134—138°, were collected. An earlier experiment had shown that, although cinchonamine was easily isolated by reason of its sparing solubility, the second product was very difficult to obtain pure (separation by means of the nitrates being unsuccessful because of the insolubility of *epi*cinchonamine

nitrate). The material was therefore subjected to fractional crystallisation from ether. The first crop was pure cinchonamine (47 mg.; m. p. 180—181°; $[\alpha]_D$ +123° (18·7 mg. in 1·04 c.c. of alcohol); mixed m. p. 182—183°; nitrate, m. p. and mixed m. p. 227° (decomp.)), but the subsequent fractionation did not effect a consistent separation of the two components, both of which are sparingly soluble in ether. One crystallisation, however, gave a mixture (14 mg.) from which *epi*cinchonamine in the form of massive prisms (6 mg.; m. p. 165—165°; mixed m. p. 166—166°; $[\alpha]_D$ +51° (5·6 mg. in 0·33 c.c. of alcohol)) was readily separable by hand. The following data permit the calculation of the approximate isolated yields of the two products as cinchonamine 47% and *epi*cinchonamine 26%. The fractions obtained by successive concentrations of the ethereal solution of the total product were: 47 mg., m. p. 180—181°; 81 mg., m. p. 147—158°; 8 mg., m. p. 161·5—162°; and 20 mg., m. p. 157—165° (this last being shown by mixed melting points to consist largely of *epi*cinchonamine). Melting points of synthetic mixtures with the stated percentages of cinchonamine were as follows: 80%, 165—175°; 50%, 143—158°; 33%, 143—152°; 20%, 145—157°.

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309. *The Action of Formaldehyde on Proteins.*

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It has been shown, confirming and extending the observations of Einhorn, that amides such as benzamide and phenylacetamide react with formaldehyde at pH 10 to give *N*-hydroxymethyl derivatives which condense with β-naphthol or its 6-bromo- or 3 : 6-dibromo-derivative. The 1-acylamidomethyl-2-naphthols so produced are hydrolysed by acids to 1-aminomethyl-2-naphthol or the corresponding bromine-substitution products.

Many proteins behave similarly with formaldehyde and the *N*-hydroxymethyl derivatives react in the presence of alcoholic hydrochloric acid with β-naphthol and its 6-bromo- or 3 : 6-dibromo-derivative to give condensation products which on hydrolysis yield 1-aminomethyl-2-naphthol or its mono- or its dibromo-derivative. Analysis of the condensation products for bromine provides a measure of the number of *N*-hydroxymethylamide groups and the results are roughly proportional to the number of amide groups in the protein molecule.

It is concluded that, under the alkaline conditions employed, formaldehyde converts some of the amide groups of the protein molecule into *N*-hydroxymethyl derivatives, but that under acidic conditions the formation of *N*-hydroxymethyl derivatives is reduced.

THE industrial importance of the products obtained by the action of formaldehyde on proteins has led to a considerable amount of work on the nature of the reactions involved and that done up to 1945 has been reviewed by French and Edsall ("Advances in Protein Chemistry," Vol. II, 1945, p. 277). One of the first proteins to be examined was collagen and it was concluded that formaldehyde condensed with the amino-groups present, forming methylene bridges (K. H. Meyer, *Biochem. Z.*, 1929, **208**, 23). Such a conclusion could not apply to those proteins which are condensed with formaldehyde in an acid medium, in view of the instability of methylenediamines under such conditions (Knudsen, *Ber.*, 1914, **47**, 2698). Later work on other proteins has produced evidence of the interaction of groups other than amino-groups. Carpenter and Lovelace (*Ind. Eng. Chem.*, 1942, **34**, 566) pointed out that casein bound more formaldehyde than could be accounted for by the amino-groups present and suggested that hydroxyl groups, phenolic or alcoholic, also reacted. Other groups suggested as taking part in the reactions are amide (Wormall and Kaye, *J. Soc. Chem. Ind.*, 1945, **67**, 75), glyoxaline (Theis, *J. Biol. Chem.*, 1944, **154**, 87), peptide (Nitschmann and Hadorn, *Helv. Chim. Acta*, 1944, **27**, 299), indole (Frankel-Conrat, Brand, and Clark, *J. Amer. Chem. Soc.*, 1937, **69**, 200), guanidyl (Frankel-Conrat, Cooper, and Olcott, *ibid.*, 1945, **67**, 950), and disulphide (Middlebrook and Philips, *Biochem. J.*, 1942, **36**, 294). Wormall and Kaye (*loc. cit.*) found that casein, zein, and arachin (ground-nut protein) united with more formaldehyde than did the corresponding deamidated proteins and concluded that the amide groups played an important part, but, as collagen and silk fibroin, which contain no amide group, can react with formaldehyde, it is clear that groups other than the amide group participate in the reaction. Much of the evidence brought forward concerning the nature of the reaction between formaldehyde and proteins is based on the uptake of formaldehyde, as determined after liberation by acid hydrolysis and steam-distillation. It is very unlikely that all the combined formaldehyde will be determined in this way; evidence of irreversibly bound formaldehyde, *i.e.*, formaldehyde not set free by acid hydrolysis, has been adduced (Swain, Kokes, Hipp, Wood, and Jackson, *Ind. Eng. Chem.*, 1948, **40**, 465), and it is known that formaldehyde may form stable compounds with some amino-acids (Frankel-Conrat,

Brandon, and Olcott, *loc. cit.*; Pictet and Sprengler, *Ber.*, 1911, **44**, 2030; Jacobs and Craig, *J. Biol. Chem.*, 1936, **113**, 759), tyrosine and tryptophan being converted in acid solution into isoquinoline and carboline derivatives.

The present paper describes attempts to produce evidence of the condensation of formaldehyde with protein-amide groups based on the isolation of compounds, which, it is reasonable to suppose, could only have been formed from such amide–formaldehyde condensation products. Einhorn (*Annalen*, 1905, **343**, 207; 1908, **361**, 113) showed that formaldehyde reacted with amides under acid conditions to give *N*-methylenebisamides of type (I), and under more alkaline conditions to give *N*-hydroxymethylamides of type (II). Compounds of types (I) and (II) were more stable than the corresponding amine derivatives, and several *N*-hydroxy

$$\underset{\text{(I.)}}{R\cdot CO\cdot NH\cdot CH_2\cdot NH\cdot CO\cdot R} \qquad \underset{\text{(II.)}}{R\cdot CO\cdot NH\cdot CH_2\cdot OH}$$

methylamides were condensed with β-naphthol in cold dilute alcoholic hydrochloric acid to give 1-acylamidomethyl-2-naphthols (III). In the presence of concentrated sulphuric acid, condensation was also effected with anisole, *p*-nitrophenol, quinol, and catechol, but such reaction condition appeared too drastic for use with proteins. We have prepared in good yields con-

(III.)

$$R\cdot CO\cdot NH\cdot CH_2\cdot N<[CH_2]_3 \qquad \text{(IV.)}$$

$$C_6H_4\cdot CH_2\cdot CO\cdot NH\cdot CH_2\cdot O\cdot CH_2\cdot C_6H_5 \qquad \text{(V.)}$$

densation products from β-naphthol, with *N*-hydroxymethylbenzamide (II; R = Ph) and *N-hydroxymethylphenylacetamide* (II; R = CH_2Ph), and hydrolysed the products, also in good yields, by warm alcoholic hydrochloric acid to 1-aminomethyl-2-naphthol.

The 1-aminomethyl-2-naphthol was not produced when β-naphthol, formaldehyde, and ammonium chloride were allowed to react in cold or warm hydrochloric acid solution, and consequently the 1-amino-2-naphthol cannot be derived from loosely bound formaldehyde and ammonia liberated by hydrolysis of the amides. Similar products prepared from 6-bromo- and 3 : 6-dibromo-2-naphthol yielded *6-bromo-* and *3 : 6-dibromo-1-aminomethyl-2-naphthol* respectively after hydrolysis. Dimethylaniline also reacts with (II; R = Ph) and (II; R = CH_2Ph) to yield p-*benz-* and p-*phenylacet-amidomethyldimethylaniline* respectively, and, although these were hydrolysed to *p*-aminomethyldimethylaniline, the yields were not so good as with β-naphthol and its bromo-derivatives. On the other hand, bisbenzanilido- (I; R = Ph) and bisphenylacetamido-methane (I; R = CH_2Ph), benzamidomethyl- (IV; R = Ph) and *1-phenylacetamidomethyl-piperidine* (IV; R = CH_2Ph), and *phenylacetamidomethyl benzyl ether* (V) did not react with β-naphthol under the conditions employed for condensation with *N*-hydroxymethylamides, and at higher reaction temperature compounds (I; R = Ph) and (I; R = CH_2Ph) gave methylenebis-β-naphthol.

As a result of these model experiments it is obvious that if a protein reacts with formaldehyde to give *N*-hydroxymethylamides (I) then such compounds should condense with β-naphthol and similar phenols to give products capable of hydrolysis to 1-aminomethyl-2-naphthol and related bases. Conversely, the isolation of 1-aminomethyl-2-naphthol from the product of condensation of β-naphthol with a formaldehyde-treated protein, would be strong evidence that the latter contained the group $-CO\cdot NH\cdot CH_2\cdot OH$ or $-CO\cdot NH\cdot CH_2R$ where R was a group readily removed during condensation under the conditions employed. When arachin (ground-nut protein) was treated with formaldehyde under alkaline conditions and then condensed with β-naphthol or its 6-bromo-derivative, it yielded products which on hydrolysis gave 1-aminomethyl- and 6-bromo-1-aminomethyl-2-naphthol respectively. Similarly, 3 : 6-dibromo-1-aminomethyl-2-naphthol was obtained by hydrolysis of the product prepared from formaldehyde-treated gluten and 3 : 6-dibromo-2-naphthol. These observations are regarded as direct evidence of the formation of *N*-hydroxymethylamide derivatives of the proteins under these conditions. The hydrolysis of the condensation products of β-naphthol, 6-bromo- and 3 : 6-dibromo-2-naphthol with formaldehyde-treated protein produced a complicated mixture from which the corresponding aminomethyl-2-naphthol is only isolated in small yield after a somewhat tedious process. Determination of bromine in the products obtained from formaldehyde-treated protein and 6-bromo-2-naphthol, however, provides a measure of the extent of condensation with *N*-hydroxymethylamides or similar reactive groups and Table I records the result obtained when the bromine determinations were made by Robertson's method (*J.*, 1915, **107**, 902). It was shown in model experiments that alcoholic sulphuric acid could be used instead of hydrochloric acid in

condensing the formaldehyde-treated protein with the bromonaphthols, and this avoided errors caused by occluded hydrochloric acid. Formaldehyde-treated silk fibroin condensed with a negligible amount of 6-bromo-2-naphthol and this is consistent with the absence of amide groups in this protein. The observation that proteins treated with formaldehyde at pH 0 contain only a very low percentage of groups which react with the naphthol was to be expected, as under these acid conditions amides form *N*-methylenebisamides (I) which, as shown above, do not react with β-naphthol. Arachin, glycinin, gliadin, and gluten, treated with formaldehyde in 1% potassium carbonate solution (pH 10) and then condensed with 6-bromo-1-naphthol, show a bromine content corresponding to reaction with approximately 13% of the amide groups present in the protein (see Table I). The discrepancy may be caused by steric factors preventing reactions between formaldehyde and hindered amide groups, or alternatively the reaction between *N*-hydroxymethylamide groups and 6-bromonaphthol may be retarded. This steric explanation finds some support from the experiments, summarised in Table II, with 3 : 6-dibromo-2-naphthol

TABLE I.

Reactions of formaldehyde-treated proteins with 6-bromo-2-naphthol.

Protein.	pH of CH_2O solution.	Found : Br, %.	No. of amide groups/10^4 g. of protein which reacted.	No. of amide groups/10^4 g. of protein (see Traill, *Chem. & Ind.*, 1950, 23).	% of amide groups which reacted.
Silk fibroin	10	0·05; 0·08	—	0	—
Arachin (ground nut)	10	1·23; 1·30	16·5	127	13·0
	0	0·40; 0·45	5·2	—	4·1
Glycinin (soya bean)	10	1·21; 1·26	15·5	119	13·0
	0	0·25; 0·28	3·2	—	2·7
Zein (maize)	10	3·25; 3·30	46	214	21·6
	0	0·22; 0·30	3·5	—	1·6
Gliadin	10	2·84; 2·78	36	307	11·7
	0	0·49; 0·52	5·8	—	2·0
Gluten	10	1·92; 2·21	31	235	13·2
Casein	10	0·65; 0·71	8·2	83	9·8

TABLE II.

Reactions of formaldehyde-treated proteins with 3 : 6-dibromo-2-naphthol.

Protein.	pH of CH_2O solution.	Found : Br, %.	No. of amide groups/10^4 g. of protein treated.	No. of amide groups/10^4 g. of protein.	% of amide groups which reacted.
Arachin (ground nut)	10	1·8	12·5	127	9·8
	0	0·4	3·2	—	—
Gliadin	10	4·1	28	307	9·1
	0	0·9	6·5	—	2·1
Zein	10	3·5	23	214	10·1
	0	0·41	3·3	—	1·6
Gluten	10	3·3	22·5	235	9·6

TABLE III.

Reaction of formaldehyde-treated arachin (ground-nut protein) under varying alkaline conditions with 6-bromo-2-naphthol.

K_2CO_3 in the hardening solution, %.	Found : Br, %.	No. of amide groups/10^4 g. of protein treated.	No. of amide groups/10^4 g. protein.	% of amide groups which reacted.
1	1·2; 1·3	16·5	127	13·0
2·5	1·6; 1·7	23	127	18·0
5	2·2; 2·3	31	127	24·4
7·5	2·2; 2·5	31	127	24·4
10	2·5; 2·6	35	127	28·0

and formaldehyde-treated proteins. The results are similar to those reported above in Table I, but the heavier naphthol derivative employed in this case inhibits the reaction, and the bromine contents at pH 10 correspond to reaction with only 10% of the amide groups present in the protein. The high values for zein, particularly the value with 6-bromo-2-naphthol, are difficult to explain; formaldehyde-treated zein dissolves in the alcohol during treatment with the bromonaphthols possibly with greater exposure of *N*-hydroxymethylamide groups to attack.

When the concentration of the potassium carbonate used in condensing the protein and formaldehyde is raised from 1 to 10% the number of hydroxymethyl groups, as measured by the bromine present after condensation with 6-bromo-2-naphthol, increases. It was observed that the protein was more dispersed in more concentrated potassium carbonate solution, and this factor, which is under further consideration, may be one facilitating reaction. Table III summarises these results.

Experimental.

N-Hydroxymethylphenylacetamide (II; R = CH_2Ph).—A suspension of phenylacetamide (50 g.) in 4% potassium carbonate solution (50 c.c.) and 40% formaldehyde solution (40 c.c.) was warmed on a water-bath for a few minutes until dissolution was complete. The *N-hydroxymethyl* compound which separated on cooling was collected after 12 hours, washed first with a little dilute sodium hydroxide solution and then with water, and dried. It crystallised from toluene in colourless plates (51 g.), m. p. 78° (Found: C, 65·8; H, 6·65; N, 8·4. $C_9H_{11}O_2N$ requires C, 65·4; H, 6·7; N, 8·5%), which were soluble in hot water, alcohol, or benzene.

1-*Phenylacetamidomethyl-2-naphthol* (III; R = CH_2Ph).—A solution of *N*-hydroxymethylphenylacetamide (5 g.) and β-naphthol (5 g.) in alcohol (50 c.c.) containing concentrated hydrochloric acid (1 c.c.) or 50% sulphuric acid (1 c.c.) was refluxed for 20 minutes. After cooling, the product was collected, and a further crop obtained by concentrating the liquors. Recrystallisation from hot alcohol gave 1-*phenylacetamidomethyl-2-naphthol* in long colourless needles (7·4 g.), m. p. 141° (Found: C, 78·0; H, 5·9; N, 5·0. $C_{19}H_{17}O_2N$ requires C, 78·3; H, 5·8; N, 4·8%). Instead of by refluxing as described above, the reaction may be carried out by keeping the mixture for 4 days at room temperature.

6-*Bromo*-1-*phenylacetamidomethyl-2-naphthol*, prepared similarly in 85% yield from 6-bromo-2-naphthol (Franzen and Staubie, *J. pr. Chem.*, 1922, **103**, 352), crystallised from alcohol in long needles, m. p. 184° (Found: C, 61·7; H, 4·4; N, 3·5. $C_{19}H_{16}O_2NBr$ requires C, 61·6; H, 4·3; N, 3·8%).

6-*Bromo*-1-*benzamidomethyl-2-naphthol*, prepared similarly in 90% yield from *N*-hydroxymethylbenzamide (Einhorn, *loc. cit.*), separated from alcohol in colourless needles, m. p. 219—220° (Found: C, 60·3; H, 3·8; Br, 22·8; N, 4·0. $C_{18}H_{14}O_2NBr$ requires C, 60·7; H, 3·9; Br, 22·5; N, 3·9%).

3 : 6-Dibromo-2-naphthol was prepared by the following modification of the method described by Franzen and Staubie (*loc. cit.*). A solution of bromine (160 g.) in acetic acid (60 c.c.) was added with shaking and cooling at 25—30° during 30 minutes to a solution of β-naphthol (72 g.) in acetic acid (220 c.c.). After 2 hours at room temperature the suspension of 1 : 6-dibromo-2-naphthol which had formed was warmed to 40—50°, and a solution of bromine (96 g.) in acetic acid (30 c.c.) added rapidly. After 2 hours on the water-bath, the product was cooled, collected, washed with acetic acid (250 c.c.) and then water, and dried in air. This crude 1 : 3 : 6-tribromo-2-naphthol (160 g.), m. p. 110—122° (Franzen and Staubie, *loc. cit.*, gave m. p. 133° for 1 : 3 : 6-tribromo-2-naphthol containing 1 mole of acetic acid), was refluxed with acetic anhydride (700 c.c.) for 3 hours. When the reaction mixture cooled to room temperature, 1 : 3 : 6-tribromo-2-naphthyl acetate (97 g.), m. p. 183—185°, separated; after crystallisation from benzene it had m. p. 187—188° (Franzen and Staubie, *loc. cit.*, give m. p. 188°). 1 : 3 : 6-Tribromo-2-naphthyl acetate (75 g.) was reduced by refluxing it for 6 hours with tin (70 g.), concentrated hydrochloric acid (200 c.c.), and alcohol (300 c.c.), and after decantation from unused tin the solution was concentrated under reduced pressure to half its volume and poured into water (2 l.). 3 : 6-Dibromo-2-naphthol (52 g.), m. p. 129—131°, separated and after crystallisation from benzene had m. p. 133—134° (Found: Br, 53·1. Calc. for $C_{10}H_6OBr_2$: Br, 52·9%) (Franzen and Staubie, *loc. cit.*, give m. p. 135°).

3 : 6-*Dibromo*-1-*benzamidomethyl-2-naphthol*, prepared in the usual way, crystallised from alcohol in stout colourless prisms, m. p. 146° (Found: C, 49·3; H, 3·2; N, 2·9. $C_{18}H_{13}O_2NBr_2$ requires C, 49·7; H, 3·0; N, 3·2%).

3 : 6-*Dibromo*-1-*phenylacetamidomethyl-2-naphthol*, prepared similarly in 80% yield, crystallised from alcohol in long colourless needles, m. p. 218° (Found: C, 50·8; H, 3·5; Br, 35·4. $C_{19}H_{15}O_2NBr_2$ requires C, 50·8; H, 3·3; Br, 35·6%).

p-*Benzamidomethyl-NN-dimethylaniline hydrochloride*, prepared from *N*-hydroxymethylbenzamide (0·5 g.) and dimethylaniline (0·4 g.) in alcohol (5 c.c.) containing concentrated hydrochloric acid (1 c.c.), separated from alcohol in long colourless needles (0·22 g.) after 20 days' storage at room temperature and had m. p. 183° (Found: C, 66·5; H, 6·8; N, 9·9. $C_{18}H_{19}ON_2Cl$ requires C, 66·1; H, 6·5; N, 9·6%).

p-*Phenylacetamidomethyl-NN-dimethylaniline hydrochloride*, prepared similarly, separated from alcohol in colourless needles, m. p. 202° (Found: C, 66·5; H, 6·8; N, 9·4. $C_{19}H_{21}ON_2Cl$ requires C, 67·0; H, 6·9; N, 9·2%).

Hydrolysis of 1-*acylamido-2-naphthol and derivatives.*

1-*Aminomethyl-2-naphthol*.—The following is a typical experiment. 1-Phenylacetamidomethyl-2-naphthol (5 g.) was refluxed for 3 hours with alcohol (100 c.c.) and concentrated hydrochloric acid (30 c.c.). The crystalline material which separated on cooling was collected, washed with alcohol, dried, and crystallised from hot water; 1-aminomethyl-2-naphthol hydrochloride (2·0 g.) separated in long needles, m. p. 224—225° (decomp.) (Found: C, 63·1; H, 5·7; N, 6·7. Calc. for $C_{11}H_{10}ONCl$: C, 63·0; H, 5·7; N, 6·7%) [Mario Betti, *Gazzetta*, 1906, **36** (1), 388, and Einhorn, *loc. cit.*, give m. p. 224—225° (decomp.)]. The *ditoluene-p-sulphonyl* derivative, prepared by warming, for 15 minutes on the water-bath, a mixture of the hydrochloride (0·2 g.), 10% sodium hydroxide solution (5 c.c.), and toluene-*p*-sulphonyl chloride (0·5 g.), crystallised from alcohol in stout prisms, m. p. 198° (Found: C, 62·7; H, 4·8; N, 3·1. $C_{32}H_{29}O_5NS_2$ requires C, 62·4; H, 4·8; N, 2·9%).

Hydrolysis of 1-benzamidomethyl-2-naphthol and *NN'*-di-(2-hydroxy-1-naphthyl)succinamide, m. p. 218° (Einhorn, *loc. cit.*), to 1-aminomethyl-2-naphthol were effected similarly.

6-*Bromo*-1-*aminomethyl-2-naphthol*.—The *hydrochloride* prepared similarly in 80% yield from 6-bromo-1-benz- or 6-bromo-1-phenylacet-amido-2-naphthol, crystallised from hot water in colourless silky

needles, m. p. 248° (decomp.) (Found: C, 46·1; H, 3·8; N, 4·85. $C_{11}H_{11}ONClBr$ requires C, 43·7; H, 3·8; N, 4·85%), which gradually became pink on exposure to the air. The base, liberated by treatment with aqueous sodium carbonate and isolated with ether, crystallised from alcohol in colourless prisms, m. p. 153° (Found: C, 52·8; H, 4·2; N, 5·7. $C_{11}H_{10}ONBr$ requires C, 52·6; H, 4·0; N, 5·5%), which rapidly became pink. The *ditoluene-p-sulphonyl* derivative crystallised from alcohol in thick colourless prisms, m. p. 208° (Found: N, 2·7; Br, 14·7. $C_{32}H_{30}O_5NBrS_2$ requires N, 2·5; Br, 14·3%).

3 : 6-*Dibromo-1-aminomethyl-2-naphthol*.—The *hydrochloride*, prepared similarly from 3 : 6-dibromo-1-benz- or 3 : 6-dibromo-1-phenylacet-amidomethyl-2-naphthol, separated from hot water in long colourless needles, m. p. 235° (Found: C, 36·3; H, 2·8; N, 3·7. $C_{11}H_{10}ONClBr_2$ requires C, 35·9; H, 2·7; N, 3·8%), which became faintly pink on exposure to air. The *ditoluene-p-sulphonyl* derivative crystallised from alcohol in short thick needles, m. p. 199—200° (Found: C, 47·3; H, 3·5; Br, 24·9. $C_{31}H_{27}O_5NBr_2S_2$ requires C, 46·9; H, 3·3; Br, 25·0%).

1-*Phenylacetamidomethylpiperidine* (IV; R = CH_2Ph), prepared by refluxing *N*-hydroxymethylphenylacetamide (2 g.) and piperidine (1·7 c.c.) in methyl alcohol (10 c.c.) for 3 hours, crystallised from alcohol in slender needles (2·2 g.), m. p. 128° (Found: C, 72·5; H, 8·4; N, 12·4. $C_{14}H_{20}ON_2$ requires C, 72·4; H, 8·6; N, 12·1%). This compound and also benzamidomethylpiperidine (IV; R = Ph), m. p. 122° (Einhorn, *loc. cit.*), were recovered after treatment with β-naphthol and 4% alcoholic hydrogen chloride at room temperature for 14 days.

Benzyl Phenylacetamidomethyl Ether (V).—*N*-Hydroxymethylphenylacetamide (3 g.) was heated for 6 hours in an oil-bath at 105—110° with benzyl alcohol (10 c.c.) containing 80% formic acid (0·5 c.c.). After removal of excess of benzyl alcohol under reduced pressure, the residue solidified on cooling and crystallised from alcohol in colourless leaflets (3·4 g.), m. p. 69—70° (Found: C, 75·0; H, 7·0; N, 5·5. $C_{16}H_{17}O_2N$ requires C, 75·3; H, 6·7; N, 5·5%). This ether was recovered after treatment with β-naphthol and 4% alcoholic hydrochloric acid for 14 days at room temperature.

Bisphenylacetamidomethane (I; R = CH_2Ph).—Phenylacetamide (5 g.), suspended in a solution at pH 6 containing saturated sodium sulphate (37·5 c.c.), concentrated sulphuric acid (11 c.c.), and 40% formaldehyde (2·5 c.c.), was heated on a water-bath. Dissolution was rapid and after a few minutes' heating the heavy white precipitate produced was collected, washed, and crystallised from alcohol; it formed long colourless needles (4·6 g.), m. p. 210° (Found: C, 72·2; H, 6·2; N, 10·4. Calc. for $C_{17}H_{18}O_2N_2$: C, 72·3; H, 6·4; N, 10·1%). Hepp (*Ber.*, 1877, **10**, 1650), who prepared this compound from benzyl cyanide and methylal in presence of acetic–sulphuric acid, gives m. p. 205°. The compound did not react with β-naphthol in presence of cold 4% alcoholic hydrochloric acid during 14 days at room temperature, but after the mixture had been refluxed methylenebis-β-naphthol, m. p. 197°, was obtained.

Bisbenzamidomethane (I; R = Ph), m. p. 216° (Einhorn, *loc. cit.*, gives 216°), prepared similarly, gave methylenebis-β-naphthol after 10 hours' refluxing with β-naphthol in alcoholic hydrochloric acid.

Isolation of 1-Aminomethyl-2-naphthol and its Bromo-derivatives from the 2-Naphthol and the Bromo-2-naphthol compounds of Formaldehyde-treated Arachin (Ground-nut Protein) and Gluten.—Arachin (ground-nut) protein. This was supplied by Imperial Chemical Industries Limited, Nobel Division, and had been prepared in the following way. The oil was removed from crushed blanched ground-nuts by solvent extraction, and the protein extracted from the resultant meal by means of 0·15% aqueous sodium hydroxide. The clarified extract was brought to pH 5·0 with sulphur dioxide, and the precipitated protein washed with water and spray-dried.

Reaction. Arachin (50 g.) was stirred for 90 minutes at 60—70° with 40% formaldehyde solution (200 c.c.), potassium carbonate (2·5 g.), and water (200 c.c.). The slime was collected, drained, and suspended in water (400 c.c.) containing a little sulphuric acid to coagulate the protein and facilitate filtration. After the protein had been washed with water and alcohol, the alcohol-wet product was suspended in alcohol (500 c.c.) containing concentrated hydrochloric acid (50 c.c.) and either (*a*) β-naphthol (25 g.) or (*b*) 6-bromo-2-naphthol (25 g.).

After being shaken at room temperature for 17 days, the protein was collected, washed with alcohol, dried, and refluxed, with stirring, for 5 hours with alcohol (400 c.c.) and concentrated hydrochloric acid (100 c.c.) (*A*). The solid (partly hydrolysed protein) was collected, the filtrate neutralised with solid sodium hydrogen carbonate, and the sodium chloride removed by filtration and the alcohol under reduced pressure. The residue was dissolved in hot ether (350 c.c.), dried (Na_2SO_4), recovered (0·5 g.), dissolved in dilute hydrochloric acid (40 c.c.), and filtered. The filtrate, was extracted with ether (3 × 25 c.c.) to remove non-basic compounds, and neutralised with sodium carbonate, and the liberated base extracted with ether (*B*). In case (*a*) removal of the ether (*B*) gave a brown viscous oil, which solidified on cooling and was identified as 1-aminomethyl-2-naphthol by conversion into the hydrochloride (35 mg.), m. p. 220—222° (decomp.), and the ditoluene-*p*-sulphonyl derivative, m. p. 198°, identical with the derivatives described on p. 1496. In case (*b*) removal of the ether (*B*) yielded a brown solid (20 mg.), m. p. 135—145°, raised to 155° by crystallisation from alcohol, which was identified as 6-bromo-1-aminomethyl-2-naphthol by comparison with the specimen prepared as described above and by conversion into the ditoluene-*p*-sulphonyl derivative, m. p. 206°. Gluten (40 g.) was similarly treated with 3 : 6-dibromo-2-naphthol (10 g.) to stage (*A*). The solution which was obtained on hydrolysis was filtered to remove a small amount of insoluble material and neutralised with solid sodium hydrogen carbonate. The precipitate was collected and the sodium chloride dissolved in water, leaving a residue (1·5 g.). This insoluble material was dissolved in aqueous sodium hydroxide and treated with toluene-*p*-sulphonyl chloride in the usual way, and the product separating from the alkaline solution was collected (30 mg.). Several crystallisations from alcohol gave the ditoluene-*p*-sulphonyl derivative of 3 : 6-dibromo-1-aminomethyl-2 naphthol, m. p. 198—199°, identical with the specimen prepared as above.

Reactions of formaldehyde-treated proteins with 6-bromo- and 3 : 6-dibromo-2-naphthol.

Reactions of Formaldehyde with Proteins at pH 10.—The protein (10 g.) was stirred for 30 minutes at 60—70° with a solution (pH 10) composed of 40% formaldehyde (10 c.c.), potassium carbonate (1 g.), and water (90 c.c.). The resulting slime was filtered off, poured into 0·5% sulphuric acid, and collected. The

precipitate was well washed with water, dried for several days, and powdered. Arachin was also condensed with formaldehyde in the presence of 2·5, 5·0, 7·5, and 10·0% of potassium carbonate. The products were worked up in the usual way and condensed with 6-bromo-2-naphthol, and the condensation product was purified and analysed for bromine.

Reactions of Formaldehyde with Proteins at pH 0.—Arachin, glycinin, gliadin, and zein (10 g.) were stirred as above at 60—70° with a solution at pH 0 composed of saturated sodium sulphate solution (73 c.c.), concentrated sulphuric acid (22 c.c.), and 40% formaldehyde (5 c.c.). The powdery products were easily collected, washed with water, and dried in a vacuum desiccator.

Reactions of Hardened Proteins with (i) *6-Bromo-2-naphthol and* (ii) *3 : 6-Dibromo-2-naphthol.*—Powdered and hardened protein (2 g.) was suspended in alcohol (10 c.c.) containing 50% sulphuric acid (1 c.c.) and 6-bromo-2-naphthol (1 g.) or 3 : 6-dibromo-2-naphthol (1·5 g.). After 14 days at room temperature, the product was collected and washed with alcohol, and unchanged naphthol removed by extraction for 8 hours with ether in a Soxhlet apparatus. The protein was finally washed well with water, dried for 3—4 hours at 110—120°, and powdered before the bromine determination. Zein, hardened at pH 0, was soluble in alcohol and the following procedure was adopted. Zein (2 g.) (hardened at pH 0), 6-bromo- or 3 : 6-dibromo-2-naphthol (1 g.), and alcohol (20 c.c.) containing 50% sulphuric acid were allowed to react for 18 days at room temperature. The protein was precipitated by dropping the solution with rapid stirring into ether, and the white resinous product was collected, washed well with ether, and dried at 80° for 1 hour. The clear hard resin was redissolved in alcohol, recovered by pouring the solution into ether, and dried first at 80° for 1 hour and finally at 110—120° for 4 hours before analysis.

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310. *The Polymerisation of Vinyl Compounds by the Sulphite Radical.*

By B. DUDLEY SULLY.

The polymerisation of styrene in emulsion by means of monothionic acid radicals generated by the oxidation of sodium sulphite in the aqueous phase is described. The polymerisation is catalysed by the presence of traces of copper in a manner parallel to the known effects of similar quantities of copper in the aerial oxidation of sulphite solutions. The proposed mechanism is in agreement with current theories for both the oxidation of sulphite and the reaction of the bisulphite ion with styrene in the presence of an excess of gaseous oxygen. It is also shown that when the partial pressure of oxygen approaches zero each atom of oxygen produces several molecules of polymer, and the effect is explained by chain transfer between the growing radical and the sulphite ions in solution. The polymer molecules formed have sulphonic acid end-groups.

THIS research began with the observation that addition of sodium sulphite to an emulsion of styrene in water markedly increased the rate of polymerisation. Further experiment showed that the rate of polymerisation increased with rising temperature, being a maximum, at atmospheric pressure, at 90°. This paper describes the polymerisation of styrene but the same technique can be applied to other polymerisable vinyl compounds such as vinyl acetate and methyl methacrylate. For example, vinyl acetate can be polymerised quite rapidly at room temperature although, as with all emulsion techniques applied to ester monomers, the product may be partly hydrolysed unless the pH of the emulsion is kept within certain limits.

The procedure in its simplest form as applied to styrene is illustrated by the following experiment: 50·0 g. of styrene (freshly distilled) containing 0·5 g. of oleic acid were emulsified with twice the weight of distilled water containing 0·50 g. of hydrated sodium sulphite. The emulsion was stirred in a flask at 90·0° $\pm$ 0·1° (thermostat) and was vented to the atmosphere through a narrow-bore glass tube about 6 in. long. In this way air could very slowly diffuse into the flask, aided to some extent by the expansion and contraction of the vapour above the emulsion caused by slight variations in the temperature of the bath. The sodium sulphite used contained 8 p.p.m. of copper and 15 p.p.m. of iron. After approximately 17 hours' stirring, polymerisation was complete and there was no residual odour of styrene. During the polymerisation about 13 g. of the styrene coagulated prematurely to a hard mass that adhered to the stirrer. The Staudinger molecular weight of the product isolated by coagulation with butanol and acetic acid, washing with distilled water and drying in an oven, was 390,000. An experiment at 80° under the same conditions gave similar results. The procedure was improved in later experiments by the following changes. (1) The oleic acid was replaced by stearic acid (this improved the colour of the product after moulding). (2) Alkali or buffer salts were added, to lessen the variation in pH that results from such causes as the formation

of benzaldehyde or the oxidation of the sulphite. (3) Protective colloids, *e.g.*, gelatin or methyl cellulose, were added to the emulsion to increase its stability. (4) The presence of protective colloids, particularly gelatin, tends to reduce the catalytic activity of the sulphite and so increase the time of polymerisation. It was realised that the oxidation of sulphite is also inhibited by the presence of gelatin and, on the assumption that the chain oxidation of the sulphite was the starting point of the polymerisation, 10 p.p.m. of cupric copper were added to increase the rate of chain initiation. Experiments 1 and 2 show the inhibiting effect of gelatin and the manner in which it is overcome.

In another series of experiments attempts were made to measure the absorption of oxygen by connecting the reaction vessel to a gas burette, but the results were not conclusive because there was a considerable apparent absorption of gas when polymerisation was nearly complete owing to removal of the partial pressure exerted by the monomeric styrene. On an industrial scale commercial nitrogen containing 0·1% of oxygen has been used to obtain a controlled oxidation of the sulphite.

The remaining experiments (nos. 3—15) were made with particularly rigid control of oxygen and oxidising impurities. A review of these experiments shows that the coupling between the oxidation of the sulphite and the polymerisation of the styrene is not so rigid as was at first thought, and leads to the conclusion that the intermediate active state is capable of separate existence for an appreciable time. In order to examine the effect of oxygen and oxidising agents it was clear that special consideration would have to be given to the purification of the styrene before polymerisation. Earlier experience had shown that by vacuum-distillation alone it is particularly difficult to obtain with absolute certainty styrene perfectly free from oxidation products, a difficulty apparently caused by very small leaks in the apparatus. The presence of aldehydic impurities in most samples of styrene distilled *in vacuo* in the laboratory can be shown by the change in colour when a sample is shaken with a small proportion of aqueous neutral 5% hydroxylamine hydrochloride solution containing methyl-orange. The best styrene samples from the point of view of oxygen impurities were prepared by steam-distillation. At first premature polymerisation caused considerable difficulty, but this was later eliminated by steam-distillation from a solution of ferrous sulphate in the presence of sulphur. Using the apparatus shown in Fig. 1 it was possible to work in the complete absence of air and the styrene could be steam-distilled under reflux and run into the polymerisation solution as and when required. At no time did polymerisation cause difficulty when this method was used.

Experimental.

The polymerisation system for experiments 1 and 2 had the following composition in parts by wt.: styrene 100, anhydrous sodium sulphite 1·0, stearic acid 0·5, gelatin 0·3, anhydrous sodium carbonate 0·05, and distilled water 300. The apparatus, a three-necked flask fitted with a thermometer and an efficient stirrer, was cleaned with chromic–sulphuric acid to remove traces of inhibitors. Recently distilled styrene containing quinol was de-stabilised by washing with (1) aqueous sodium hydroxide until no colour was developed in the alkali after keeping for ½ hour, (2) distilled water, (3) 0·1*N*-potassium dichromate acidified with acetic acid, and finally (4) several quantities of distilled water until neutral. The emulsion was prepared within 1 hour of de-stabilising the styrene and was heated in a water-bath thermostatically controlled to 90·0° ± 0·1°. A temperature of 60° was reached in less than 5 minutes and time readings were referred to this point as zero. Samples of the emulsion were drawn at zero time and at 15-minute intervals until polymerisation had commenced as shown by the formation of an opalescence on dilution with an excess of methanol. After the induction period had been determined further samples were taken at hourly intervals. The amount polymerised was determined by precipitating the emulsion with a ten-fold excess of methanol acidified with hydrochloric acid to *N*/100. The polymer was washed with methanol, followed by *N*/1000-acetic acid and a further quantity of methanol, after which it was dried at 80° and weighed. The rate of oxidation of the sulphite was estimated by diluting a sample of the emulsion with ten times its weight of distilled water, neutralising with acetic acid, and titrating with *N*/10-iodine (starch).

Experiment 1.—No added copper catalyst.

Time (hrs.)	0	1	2	2·25	3	4	5	22
Temp.	60·0°	89·8°	89·8°	89·3°	89·5°	89·8°	89·5°	89·5°
Wt. polymerised, %	0	0	0	trace	0·20	—	2·5	39·4
Sodium sulphite (parts by wt.)	1·000	0·930	0·920	—	0·870	0·850	0·805	0·426

Experiment 2.—Conditions as in expt. 1 except for the addition of copper sulphate equivalent 10 p.p.m. of metallic copper, calc. on the wt. of styrene.

Time (hrs.)	0	0·25	0·5	1	2	2·5	3	3·5	4	5	6
Temp.	60°	87°	89·8°	89·2°	90·0°	90·0°	90·2°	90·8°	91·0°	90·1°	89·8°
Weight polymerised, %	0	trace	2·4	8·56	22·5	—	46·6	—	82·8	100	—
Sodium sulphite (parts by wt.)	1·000	0·944	0·895	0·845	—	0·760	0·730	0·674	0·654	0·495	0·332

The molecular weight of the polymer formed in expt. 2 as determined by the Staudinger viscosity method was 117,000. It will be observed that during the polymerisation 0·4 g. of sodium sulphite was oxidised and on the assumption that one molecule of sulphite would on oxidation lead to the formation of one molecule of polystyrene the number-average molecular weight is $100 \times 126/0{\cdot}4 = 31{,}500$, which is not inconsistent with available data. Other similar experiments showed that the rate of polymerisation was influenced by the pH of the sulphite solution in a manner parallel with the influence of pH on the rate of oxidation of sulphite solutions by gaseous oxygen.

Experiments 3—15.—Materials used were:

(a) *Styrene.* Pure styrene stabilised with quinol and sulphur, n_D^{20} 1·54697.

(b) *Sodium sulphite, anhydrous.* Iron content 30 p.p.m.; copper content 15 p.p.m.

(c) *Copper sulphate, N/10.* Standardised by Foote's method (*J. Amer. Chem. Soc.*, 1938, **60**, 1349).

(d) *Stearic acid.* Good-quality commercial acid having an iodine value less than 5 and a faint yellow colour when molten [Type S.D.S., Prices (Bromborough) Ltd.].

(e) *Distilled water.* Obtained by distillation of town water with sodium chromate using an aluminium condenser, it contained up to 10 p.p.m. of aluminium.

(f) *Ferrous sulphate.* Analar grade.

(g) *N-Sodium hydroxide.* Standard laboratory analytical reagent.

FIG. 1.

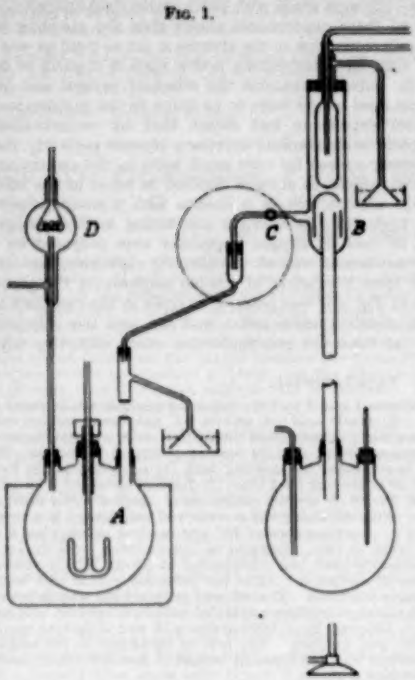
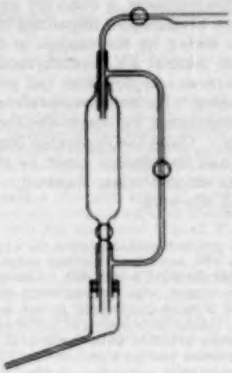


FIG. 2.



Apparatus. The apparatus (Fig. 1) consisted of a three-necked flask (*A*) fitted with a glass stirrer in a stainless steel bearing with a rubber gland and an inlet for the styrene. The whole was immersed in a bath at 91·0° (thermostat). The styrene was steam-distilled in a current of hydrogen (30 ml./min.) through a specially designed column containing a separator (*B*) in the head, whereby the aqueous layer was returned to the top of the column and the styrene layer was run as required, through a stop-cock (*C*), directly into the polymerisation flask (*A*). The air in the apparatus was displaced by hydrogen from a cylinder, from which the last trace of oxygen was removed by passage through the heated filament of a 60-watt electric lamp (*D*).

General procedure. Styrene was added to the distillation flask, together with an aqueous solution of ferrous sulphate. The mixture was prevented from bumping by adding a few pieces of alumina and a little stearic acid to emulsify the styrene. The column was a Dufton spiral, 5 ft. long, and equivalent to 5—10 theoretical plates. The average composition was: styrene 160 ml.; ferrous sulphate 10 g.; stearic acid 0·5 g.; water 400 ml. The air in the flask and column was displaced with purified

hydrogen through a water seal before the heating was commenced. A manometer in the gas supply to the burner facilitated the day-to-day reproduction of the same conditions of reflux.

The polymerisation flask (*A*) contained the aqueous catalyst solution, the standard composition being sodium sulphite (anhydrous) 3·0 g., stearic acid 1·2 g., 0·1M-copper sulphate 0·6 ml., N-sodium hydroxide 1·2 ml., and distilled water 600 ml. The stearic acid was added first, followed immediately by the sodium sulphite dissolved in the full amount of water. The copper sulphate solution, followed by the sodium hydroxide, was added after the sulphite solution had reached the temperature of the thermostat (90°). The mixture was left in the thermostat with occasional stirring for an average of 17 hours before addition of the styrene, and during this time the last trace of oxygen was presumed to be absorbed by the sulphite. Continuous stirring was commenced about 1 hour before the first addition of the styrene. In order to standardise the conditions the styrene was boiled under total reflux for 3 hours before it was added to the sulphite solution. After polymerisation the emulsion was not exposed to air until it was quite cool, to avoid degradation. Prematurely coagulated polystyrene was removed by filtration through muslin. The emulsion was acidified with concentrated hydrochloric acid, and the coagulated polystyrene filtered off and washed with distilled water until free from traces of chlorides and sulphate.

Experiment 3. Styrene (100 ml.), and water (400 ml.) containing hydrated ferrous sulphate (10 g.) were boiled under total reflux for 3 hours in a current of hydrogen (30 ml./min.). The aqueous catalyst solution contained sodium sulphite (anhydrous; 3·0 g.), 0·1M-copper sulphate (0·6 ml.), stearic acid (1·2 g.), N-sodium hydroxide (1·2 ml.), and water (600 ml.). This mixture was left overnight at 91·0° and then stirred for 15 minutes; at the end of the refluxing period the styrene was added at a steady rate during 45 minutes. Stirring was continued for a further 2 hours and the emulsion was cooled overnight. Hydrogen (60—70 ml./min.) was passed through the polymerisation flask throughout the experiment. On pouring of the emulsion through muslin, 1 g. of prematurely coagulated material was obtained as a single piece. The emulsion (710 g. containing 12·3% of solid, determined by evaporation) was coagulated with hydrochloric acid. The resulting polystyrene after washing was dried in a vacuum oven at 100°. The dry polymer had a Standinger molecular weight of 605,000 and the viscosity of a 5% solution in benzene at 20° was such that a ¼ in. steel ball took 47 seconds to fall through 6 cm.

Experiment 4. In this experiment no copper catalyst was added, the only copper metal present being that contained as impurities in the components, particularly the sodium sulphite. The general conditions were as in expt. 3. The resulting emulsion contained 12·7% of polystyrene and 1 g. of prematurely coagulated material. The product, isolated as before, had a Staudinger molecular weight of 583,000 and the viscosity of a 5% solution measured as in expt. 3 was 36 seconds.

Experiment 5. This experiment was made to determine the activity of sodium dithionate as a catalyst for polymerisation. The sodium dithionate was recrystallised 3 times from water and was free from chloride and sulphate. The general conditions were similar to those of expt. 3. A solution containing sodium dithionate (3·0 g.) and stearic acid (1·2 g.) in water (600 ml.) was kept at 91° for 45 hours in a current of hydrogen (60—70 ml./min.). N-Sodium hydroxide (1·2 ml.) was then added. The styrene was boiled under reflux for 3 hours and then distilled into the polymerisation flask during 105 minutes. After a further 4 hours the emulsion was allowed to cool overnight. Next morning the styrene had separated and appeared to be only slightly polymerised. A small proportion remained emulsified in the water but contained only 10% of polystyrene, the remainder being unchanged monomer.

Experiment 6. Expts. 6, 7, and 8 were made to determine whether it is necessary to have the copper catalyst present in the emulsion throughout the polymerisation or whether the monothionic acid radicals or radical ions have an appreciable life before dimerisation. The general conditions were as in expt. 3. Sodium sulphite (anhydrous; 3·0 g.), 0·1M-copper sulphate (10·0 ml.), and N-sodium hydroxide (3·2 ml.) were dissolved in water (600 ml.) at 70° and the solution was filtered in air through a Buchner funnel to remove the cuprous precipitate. It was then poured immediately into the polymerisation flask which already contained stearic acid (0·5 g.) and from which all air had been displaced by a current of hydrogen. The styrene, which had been boiling under reflux for 3 hours, was added at a constant rate during 2 hours. The product had a Staudinger molecular weight of 394,000 and the viscosity of a 5% solution measured as in expt. 3 was 30 seconds.

Experiment 7. This experiment was similar to the previous but the apparatus was modified so that the mixing and filtration of the sodium sulphite solution after the addition of the copper could be carried out in an atmosphere of purified hydrogen, at 90°. The polymerisation proceeded exactly as before and the product had a Staudinger molecular weight of 533,000.

Experiment 8. This experiment was again similar to experiment 5 but 50 ml. of styrene monomer were added to the sulphite solution after the addition of the copper sulphate solution. The temperature was 90° throughout. The styrene monomer separated all the precipitated cuprous oxide by a kind of flotation process so that on filtration through paper in an atmosphere of purified hydrogen every detectable trace was removed. Styrene added to the filtrate polymerised as readily as before and the polymer produced gave a clear moulding free from copper. It appears that the sulphite radicals remain in the solution and will catalyse the polymerisation even after the removal of the metals.

Experiment 9. A solution containing sodium sulphite (anhydrous; 3·0 g.), stearic acid (1·2 g.), N-sodium hydroxide (1·4 ml.), and 0·1M-copper sulphate (1·0 ml.) in air-free water (600 ml.) was allowed to remain in a hydrogen atmosphere for 48 hours at 90° in an unsuccessful attempt to prevent polymerisation by allowing the sulphite radicals to dimerise. Styrene was added during 2 hours and was completely polymerised in a further hour. The emulsion contained 13·0% of polymer after passing through a muslin screen which retained 1 g. The Staudinger molecular weight was 722,000 and the viscosity of a 5% solution measured as before was 94 seconds.

Experiment 10. This experiment was similar to expt. 3, except that the catalyst solution was kept at 90° for 17 hours before addition of the styrene and commercial nitrogen was used as the inert gas. The styrene polymerised readily to a Staudinger molecular weight of 583,000.

In the remaining experiments the apparatus was so modified that the styrene could be collected and

measured before being added to the sulphite solution. To do this the portion of the apparatus enclosed in the circle in Fig. 1 was modified as shown in Fig. 2. Care was still taken to ensure that oxygen contamination was eliminated by thorough purging of the apparatus with measured volumes of purified hydrogen.

Experiment 11. The general conditions were similar to those described in the previous experiments but the amount of copper catalyst was reduced. Stearic acid (1·2 g.) and hydrated sodium sulphite (6·0 g.) were weighed into the polymerisation flask. The air in the flask was displaced with hydrogen, and then 600 ml. of boiling distilled water containing N/100-copper sulphate in 1% acetic acid (0·18 ml.) and N-sodium hydroxide (2·0 ml.) were added. The solution was left overnight in contact with purified hydrogen. The styrene was first boiled under reflux in hydrogen for 2½ hours and then 120 ml. were collected in a current of hydrogen and run into the catalyst solution during 1½ hours. Polymerisation was complete about ½ hour after the last drop had been added, and the emulsion was allowed to cool overnight. The emulsion contained 15·6% of polymer and 7 g. of coarse particles retained by a muslin screen.

Experiment 12. Stearic acid (1·2 g.) and hydrated sodium sulphite (6·0 g.) were added to the flask as in the previous experiments, followed by 600 ml. of boiling distilled water containing N/100-copper sulphate in 1% acetic acid (0·18 ml.) and N-sodium hydroxide (10 ml.). After 3 hours' refluxing in hydrogen, 200 ml. of the styrene were collected and run into the polymerisation solution during 3 hours. 45 Minutes after the last drop of styrene had been added the unpolymerised material was distilled off in a current of hydrogen. After recovery of 33 ml. of styrene in this way the mixture was left to cool overnight. Distillation was recommenced the next morning and a further 16 ml. of styrene were obtained, making a total of 49 ml. The final emulsion (650 g.) was alkaline to phenolphthalein and contained 18·6% of polymer having a Staudinger molecular weight of 455,000.

In the next experiment the general quantities and conditions were as in expt. 12, but the reaction time was considerably extended in an endeavour to complete the polymerisation. However, the proportion of styrene polymerised was not greatly increased by prolonged contact with sulphite solution, owing presumably to the removal of the sulphite radicals by the formation of polystyrene.

Experiment 13. The catalyst solution prepared as in the previous experiment was stirred for 2½ hours before addition of the styrene, whereas previously the solution was left overnight. The styrene was added initially at the rate of 5 drops per minute and then at a slower rate overnight. By the next morning 80 ml. had been added. During the following day the remainder of the styrene was added, making a total of 200 ml. Since the polymerisation was not complete at the end of the day it was allowed to continue overnight. Next morning 32 ml. of unpolymerised styrene were recovered by distillation in a current of hydrogen. Coarse particles (27 g.) were separated by pouring the emulsion (710 g.) through a muslin screen. The Staudinger molecular weight of the product was 290,000 and the viscosity of a 5% solution in benzene measured as before was 3 seconds.

Experiment 14. Hydrated sodium sulphite (6·0 g.) and stearic acid (3·0 g.) were added to the flask immersed in the bath at 90° and the air was displaced with hydrogen. N/100-Copper sulphate (0·54 ml.) and N-sodium hydroxide (7·5 ml.) were added in cold distilled water (375 g.). The mixture was left overnight without stirring, in an atmosphere of purified hydrogen. Next day the solution was stirred for 4 hours, after which 75 ml. of styrene were added in 10 minutes, and were polymerised in about 30 minutes. 75 Ml. of distilled water saturated with air at 24° were next added, followed by a further 75 ml. of styrene which were run in during 15 minutes. This second portion was polymerised in a further hour, and so again 75 ml. of air-saturated water were added, followed by 75 ml. of styrene which were polymerised in about 1½ hours. A further 75 ml. of air saturated distilled water were then added, followed by 75 ml. of styrene. In this way a total of 300 ml. of styrene were added to 600 ml. of catalyst solution. After cooling overnight unchanged monomer (26 ml.) was recovered by distillation in hydrogen. The emulsion (785 g.) contained 29·1% of polymer. When the mixture was poured through muslin a single piece of polymer (10 g.) was separated. The Staudinger molecular weight was 528,000 and the viscosity of a 5% solution measured as before was 42 seconds.

Experiment 15. In this experiment the pH of the emulsion was stabilised by the use of borax, phosphate buffers having been found to interfere with the polymerisation (probably by the formation of complex salts with the copper catalyst).

Hydrated sodium sulphite (6·0 g.) and stearic acid (3·0 g.) were weighed into the polymerisation flask immersed in a bath at 90° as before, and the air was displaced with purified hydrogen. Distilled water (375 g.) containing AnalaR borax (0·60 g.) and N/10-copper sulphate (0·27 ml.) was added and the whole left in the bath overnight. Next morning the solution was stirred whilst the styrene was boiled under reflux for 2½ hours, after which the first 75 ml. of styrene were collected and added as in the previous experiments during 90 minutes. After all had been added, 75 ml. of air-saturated distilled water were run in. This process of alternate addition was repeated as in expt. 14 until a total of 300 ml. of styrene had been added and the total weight of water including that present initially was 600 ml. After 6 hours from the first addition of styrene the flask was removed from the bath and allowed to cool overnight. Next morning unchanged styrene (40 ml.) was recovered by distillation at 90° in a current of hydrogen. The polymer content of the emulsion was 27% and the coarse particles, separated on pouring through muslin, weighed 5 g. The Staudinger molecular weight of the polymer isolated as before was 527,000. The viscosity of a 5% benzene solution was 29 seconds.

All molecular weights were determined by the Staudinger viscosity method at a concentration of 0·1% of the polymer in dry benzene and a value of $1{\cdot}8 \times 10^{-4}$ for the Staudinger constant was used.

Discussion.

Polymerisation experiments of the kind described are very susceptible to the presence of traces of impurities and very rigid control is necessary before they can be considered quan-

titatively. The purest obtainable monomer was used to reduce the possibility of chain termination by reaction with an impurity. Interpretation of the experiments would be greatly simplified if it were possible to polymerise the styrene in a special solvent or with some addition functioning as a chain-terminating agent so that throughout the experiment all the polymer chains would be terminated by a controllable mechanism. At present, however, it is uncertain whether any agent exists which will affect only the chain-terminating mechanism without at the same time having an effect on the chain-initiating mechanism. Thus alcohols which cause chain termination also inhibit the oxidation of sulphite.

The oxidation of sulphite solutions by gaseous oxygen or air was first studied by Bigelow (*Z. physikal. Chem.*, 1898, **26**, 493) who showed that various organic compounds containing a hydroxyl group (*e.g.*, benzyl alcohol, butan-2-ol, allyl alcohol, mannitol, and glycerol) acted as powerful negative catalysts; he also showed that the rate of oxidation was very sensitive to the previous history of the water in which the sulphite was dissolved. Titoff (*ibid.*, 1903, **45**, 641) showed that the oxidation was very sensitive to the presence of copper and to a lesser extent of iron. One part of copper in 16×10^8 parts of water accelerated the reaction about 30%; in later work he used known amounts of copper and was then able to obtain reproducible results. Bäckström (*J. Amer. Chem. Soc.*, 1927, **49**, 1460; *Trans. Faraday Soc.*, 1928, **24**, 601) was the first to recognise the oxidation of sulphite as a chain reaction in which an active centre serves as the starting point for the oxidation of a large number of molecules. According to Semenoff ("Chemical Kinetics and Chain Reactions," Oxford Univ. Press, 1935, p. 383) it is considered by some that in the absence of both light and catalysts the oxidation of sulphite would not proceed at all. Similar conditions govern the polymerisation of styrene emulsions in sulphite solution, and in the same way it has been found impossible to purify the ingredients to such an extent that the initial polymerisation is completely inhibited.

The chain mechanism for the oxidation of sulphite involves the formation of unstable intermediate compounds either by the step-wise reduction of oxygen or by the oxidation of the sulphite ion. The latter mechanism, reviewed by Hammett ("Physical Organic Chemistry," New York, 1940, p. 370 *et seq.*), is more in accordance with the polymerisation reaction. Fuller and Crist (*J. Amer. Chem. Soc.*, 1941, **63**, 1644) found that the reaction of sodium sulphite solutions saturated with oxygen was strictly of the first order with respect to sulphite-ion concentration and was also directly dependent on the cupric ion concentration when this exceeds 10^{-6}M. From an analysis of the latter effect it was claimed that there was a primary process independent of the heavy-metal ion. It was also found that the rate is independent of the pH between 8·8 and 8·2 and decreases in a complicated manner between 5·9 and 3·2. When a solution of sodium sulphite is oxidised with an excess of oxygen only a small proportion of dithionic acid is formed, which indicates that the oxygen reacts more rapidly with the sulphite radicals than with the reduced copper. On the other hand, it has been found that the reaction of sodium sulphite with a cupric copper salt in the absence of oxygen produces a complex salt of copper which undergoes electron transfer and forms sulphite radicals, about half of which dimerise to dithionic acid.

Compounds of sodium hydrogen sulphite and styrene have been prepared by several workers. Kharasch, Schenck, and Mayo (*ibid.*, 1939, **61**, 3092) and Kharasch, May, and Mayo (*J. Org. Chem.*, 1938, **3**, 175) have studied the reaction in detail and have isolated three different compounds, *viz.*: $C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}SO_3H$, $C_6H_5{\cdot}CH{:}CH{\cdot}SO_3H$, and $C_6H_5{\cdot}CH(OH){\cdot}CH_2{\cdot}SO_3H$. These are formed simultaneously by passing oxygen into a vigorously stirred mixture of styrene with a stoicheiometric excess of alkali hydrogen sulphite. A free-radical mechanism was proposed for their formation by Kharasch and his co-workers (*locc. cit.*), who further noted that no polymer was formed during the preparation, and the present work shows that this is explained without doubt by the presence of an excess of gaseous oxygen which combines with the activated styrene radicals and prevents chain growth. The following mechanism for the polymerisation of styrene is consistent with the data for the oxidation of aqueous sulphite solutions and also with the mechanism proposed by Kharasch and his co-workers for the formation of the styrene sulphonic acid compounds:

(1) The bivalent sulphite ion loses an electron and becomes a univalent sulphite free radical, *e.g.*, monothionic acid free radical or monothionic acid free-radical ion. In the presence of bivalent copper this is explained by the formation of a complex cupric sulphite, followed by the transfer of an electron from the sulphite ion to the copper ion, as in the formation of free iodine from cupric iodide. In both cases the cupric copper is reduced to the cuprous state.

$$Cu^{++} + SO_3^{--} = Cu^{+} + SO_3^{-}\ ^{\bullet}$$

(2) The monothionic acid free radical (or free-radical ion) combines with styrene monomer to form a free radical complex.

$$C_6H_5{-}CH{=}\overset{\bullet}{C}H_2 + SO_3^{-\bullet} = C_6H_5{-}H\overset{SO_3^-}{C}{-}\overset{\bullet}{C}H_2$$

(3) The free radical complex combines with more styrene and the chain grows into a giant polymer radical by the accepted mechanism.

(4) The giant polymer radical continues to add styrene molecules linearly until it either gains or loses an electron. This may occur in various ways, *e.g.*: (*a*) Reaction with another polymer radical leading to complete termination of chain growth either by disproportionation to two neutral molecules or by dimerisation. A sulphite radical in the aqueous phase could also react similarly with a polymer radical. (*b*) Reaction with another neutral molecule. In this case the chain growth does not stop but undergoes transfer since the resulting product will still have an odd electron. The neutral molecule may be another " dead " molecule which may lose an electron from the middle of the chain leading to chain branching. The evidence adduced later in this work suggests that the most frequent reaction is the acquisition of an electron from a sulphite ion in the aqueous phase. This terminates the growth of the polymer molecule and creates another sulphite radical which in turn starts the growth of another chain.

(5) New chains are started when the trace of molecular oxygen in the gaseous phase oxidises the colloidal cuprous hydroxide back to the cupric state in which form it can react again with the sulphite ion as in (1). From this it will be seen that by the most efficient use of the oxygen in the gas space one molecule of oxygen will generate four sulphite free radicals:

$$4CuOH + 4H_2O + O_2 = 4Cu(OH)_2 + 2H_2O$$
$$Na_2SO_3 + Cu(OH)_2 = CuOH + NaOH + NaSO_3^{\bullet}$$

One of the features of the sulphite method of polymerisation is that it is particularly easy to obtain products of unusually high molecular weight. Several factors appear to contribute to this technically desirable effect, of which perhaps the most important is that the oxygen content of the emulsion is maintained at a very low value on account of its rapid reaction with the sulphite. From a general consideration it is believed that the presence of molecular oxygen is the most common factor leading to the formation of polymer molecules of low molecular weight, and the usual peroxide catalysts have obvious disadvantages in this respect. The molecular weight of the polymer may be varied by controlling the rate of oxidation of the sodium sulphite, as, for example, by passing at a measured rate through the emulsion a current of commercial nitrogen containing 0·1% of oxygen.

Several unsuccessful attempts were made to prepare a sulphite-styrene emulsion under conditions which would eliminate the initial oxidation of the sulphite, so that the polymerisation of the styrene would be completely inhibited until a trace of oxygen was admitted, but in every case the styrene polymerised to some extent before the admission of the oxygen. Attempts were also made to stir the sulphite solution in a closed system (expts. 9 and 10) so that the last trace of oxygen would be absorbed and then to allow a further lapse of time to permit the sulphite radicals to dimerise. This also was unsuccessful, for on adding the oxygen-free styrene once again a certain proportion polymerised.

The quantitative aspect of the dimerisation of a sulphite free-radical ion is interesting. If a sulphite free-radical ion dimerises immediately on collision with another similar free radical, as would be expected if the energy of activation for the combination were zero, then the concentration of radicals would decrease at a rate which at any instant is proportional to the square of the concentration at that instant (second-order reaction). Calculation on this basis shows that if at zero time the concentration is 100 and if after one minute this is reduced to 10, then the concentration after t minutes is $100/(9t + 1)$. It follows that in spite of the initial rapid reaction the amount present after one hour is still 0·185 and after 24 hours 0·0077.

On the other hand, for a unimolecular reaction in which the concentration decreased from 100 to 10 in the first minute the concentration after time t is $100 \times 0{\cdot}1^t$, so that the concentration remaining would be 0·1 in 3 minutes and 0·001 in 6 minutes. The energy of activation required for the dimerisation will not be zero owing, amongst other things, to the repelling effect of the charge on the ions which would hinder their collision. In the light of these considerations the experimental results are not altogether unexpected.

Although efforts to eliminate the radicals by mutual recombination did not succeed it was found that, unless the sulphite solution was reactivated with air or oxygen, only a limited proportion of styrene could be polymerised. Thus, in experiments 12 and 13 with the purest obtainable monomer it was found that a sulphite solution will only polymerise about one-

seventh of its weight of styrene, after which the reaction practically ceases. With very impure styrene only a small concentration of polymer can be obtained. The reaction of the sulphite free-radical ions with the styrene is probably kinetically of the first order, owing to the excess of styrene, so that the removal of the free radicals by this mechanism is readily understood.

Experiments 13, 14, and 15 show that after the removal of the free radicals from the solution by polymer formation the oxygen contained in one volume of air-saturated water at room temperature will regenerate sulphite free-radical ions in a quantity sufficient to polymerise one volume of styrene. One litre of air-saturated water at 25° contains 6·0 ml. of oxygen (N.T.P.). If one atom of oxygen leads to the formation of two sulphite free radicals, it follows that the lower possible number average molecular weight of the product is numerically equal to the weight of polymer produced by 8 g. of oxygen, *i.e.*, $22{,}400 \times 904/(8 \times 4) = 850{,}000$ approx. (the density of styrene is 904 g./l.). There is little doubt that the number average molecular weight is much less than this. It seems therefore that with the purest obtainable styrene there is considerable reaction between the growing polymer molecules and sulphite ions in solution. These sulphite ions terminate the growth of the polymer molecule by a chain-transfer mechanism in which an electron is given up by the sulphite to the growing polymer chain in the same way as it can give up an electron to cupric copper. This produces another sulphite free radical which will initiate the formation of another polymer chain.

The probability of such a reaction occurring is high, since the sulphite ions are relatively numerous and furthermore they donate an electron with relative ease. In this way several polymer molecules each containing a sulphonic acid end-group can be produced from a single molecule of oxygen as the initiating step, and the minimum amount of gaseous oxygen required to oxidise the trace of copper and so continue the polymerisation is reduced to that necessary to replace the radicals that are lost by dimerisation. Further support for this view is obtained from an estimation of the number of sulphonic acid end-groups by neutralisation with alkali and then titration with hydrochloric acid in benzene, using the viscosity of the solution to determine the end-point (Sully, *Nature*, 1947, **159**, 882). This method which is applicable to polymers of the highest molecular weight indicates a number average molecular weight of 30,000, so that under conditions of minimum oxygen consumption it seems that 850,000/30,000 = 28 molecules of polymer each containing a sulphonic acid end-group are formed from each initiating radical. However, the quantitative interpretation of the end-group titrations is as yet not quite clear and the results must be accepted with caution.

The work described above [cf. B.P. 582,134, 582,327, 587,455, and 608,635 (Sully and A. Boake, Roberts, and Co.)] forms part of an independent discovery of the so-called redox system of polymerisation. The sulphite–oxygen system described is simpler than other systems involving peroxides, so that the mechanism was appreciated at an early date. Furthermore the radicals are utilised more efficiently in the polymerisation, so that the experiments permit a quantitative interpretation not possible with systems involving peroxides in which several species of initiating radicals may be formed.

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311. *Indoles. Part II. The Preparation and Oxidation of the* Bz-*Nitro-2-methyl-3-ethyl-, -2 : 3-diphenyl-, and -2-methyl-3-phenyl-indoles.*

By K. Schofield and R. S. Theobald.

The compounds named in the title have been prepared by the Fischer indole synthesis, and their oxidation to the related propiophenones and benzophenones (I ⟶ II) has been examined. This method provides a practicable route to the nitro-2-aminobenzophenones, but not to nitro-2-aminopropiophenones. The proportions of the 4- and 6-nitroindoles formed from the *m*-nitrophenylhydrazones used have been ascertained, and are briefly discussed.

The aim of the work to be described in this series of papers is twofold: to examine the oxidative ring-fission of indole derivatives (I ⟶ II) as a source of substituted 2-aminoarylketones, and to collect data concerning the Fischer indole synthesis in its application to *m*-substituted arylhydrazones and to arylhydrazones of unsymmetrical ketones.

In Part I (*J.*, 1949, 796) we established the convenience of such oxidation of *Bz*-nitro-2 : 3-dimethylindoles (I; R = R′ = Me; R″ = NO_2) in preparing the four nitro-2-amino-

acetophenones, and showed that the cyclisation of methyl ethyl ketone *m*-nitrophenylhydrazone in hot concentrated hydrochloric acid gave a larger proportion of 6- than of 4-nitro-2 : 3-dimethylindole. The present paper describes experiments on the Fischer synthesis of indoles (I; R′ = Et or Ph; R″ = NO_2), and on the oxidation of these compounds.

Under conditions similar to those used in Part I (*loc. cit.*), methyl *n*-propyl ketone *o*- and *p*-nitrophenylhydrazones were cyclised to 7- and 5-nitro-2-methyl-3-ethylindole (as is proved below), in yields of 27% and 45% respectively based on the parent nitroanilines. The homogeneity of both products was established chromatographically. The corresponding *m*-nitrophenylhydrazone produced 33% of a mixture of isomeric indoles, m. p. 170—171° and 163—164°, in the approximate ratio 1 : 0·3, as was shown by the ready separation of the compounds on activated alumina. As with the 2 : 3-dimethylindoles, separation could not be satisfactorily accomplished by crystallisation, only a portion of the more abundant isomer being isolable by this method.

Oxidation of these indoles with chromic acid in acetic acid occurred vigorously, and as a result yields in this step were lower than in the similar oxidation of nitro-2 : 3-dimethylindoles. Recovery of 3-nitro-2-acetamidopropiophenone from 7-nitro-2-methyl-3-ethylindole was 6%, based on *o*-nitroaniline. The indoles, m. p. 170—171° and 163—164°, similarly provided 4- and 6-nitro-2-acetamidopropiophenone, giving on hydrolysis the related amines. The base from the first mentioned indole gave, by deamination, reduction, and acetylation, *p*-acetamidopropiophenone, its constitution being thus proved.

The oxidation of 5-nitro-2-methyl-3-ethylindole proved to be anomalous, providing a mediocre yield of a substance, m. p. 171—172°, different from 5-nitro-2-acetamidopropiophenone (m. p. 145—145·5°; Keneford and Simpson, *J.*, 1948, 354). The nature of this product has not yet been established, but it may be merely a polymorph of 5-nitro-2-acetamidopropiophenone since acid hydrolysis converted it into 5-nitro-2-aminopropiophenone. The present method is clearly not a practicable one by which to prepare the nitro-2-aminopropiophenones.

Clearly, nitrophenylhydrazones of methyl *n*-propyl ketone are cyclised by fuming hydrochloric acid to give only derivatives of 2-methyl-3-ethylindole, no 2-propylindoles being detected. Methyl *n*-propyl ketone phenylhydrazone is likewise converted by cuprous chloride into 2-methyl-3-ethylindole (Arbusov and Fruhauf, *J. Russ. Phys. Chem. Soc.*, 1913, **45**, 694; Arbusov and Rotarmel, *J. Gen. Chem. Russia*, 1932, **2**, 397), although Fischer (*Annalen*, 1886, **236**, 128), using zinc chloride, may have obtained a small amount of the alternative product. It does in fact seem to be generally the case that in the Fischer reaction a methylene group reacts rather than a methyl group (Buu-Hoï and Royer, *Rec. Trav. chim.*, 1947, **66**, 305), a small proportion only of the alternative product being formed as in the cyclisation of methyl ethyl ketone phenylhydrazone by nickel chloride (Korczynski, Brydowna, and Kierzek, *Gazzetta*, 1926, **56**, 903).

It is also clear that the cyclisation of methyl *n*-propyl ketone *m*-nitrophenylhydrazone is similar to that of the methyl ethyl compound (Part I, *loc. cit.*), proceeding mainly *para* to the nitro-group.

5-Nitro-2-aminobenzophenone is the only mononitro-2-aminobenzophenone so far described which contains the nitro- and amino-groups in the same ring. Its formation from 2-chloro-5-nitrobenzophenone and ammonia under pressure (Ullmann and Mallet, *Ber.*, 1898, **31**, 1694) is sluggish, and the method does not appear to be of general applicability. Oxidative fission of suitable indoles promised to be useful in this connection. Fennel and Plant (*J.*, 1932, 2872) prepared 5-nitro-2 : 3-diphenylindole from benzyl phenyl ketone *p*-nitrophenylhydrazone, and from the corresponding *m*-isomer obtained two products, m. p. 227° and 205°, which were not oriented.

We have repeated these preparations, as described in the Experimental section, and in the case of benzyl phenyl ketone *m*-nitrophenylhydrazone found, like Fennel and Plant (*loc. cit.*), that the two indoles formed were readily separated by crystallisation. Chromatography established the proportions of the compounds, m. p. 227° and 205°, in the mixture as approximately 1 : 2. On oxidation they gave 4- and 6-nitro-2-benzamidobenzophenones, respectively,

and 5-nitro-2 : 3-diphenylindole similarly gave the 5-nitro-isomer, all these ketones being formed in high yield. The structures of 4- and 6-nitro-2-benzamidobenzophenones were established by successive hydrolysis, deamination, and reduction to *p*- and *o*-aminobenzophenone, and this proof shows that the nitration products of 1-acyl-2 : 3-diphenylindoles (Fennel and Plant, *loc. cit.*) are 6-nitro-1-acyl-2 : 3-diphenylindoles. Further, if the amounts of the isomeric indoles isolated are truly indicative of the course of the cyclisation, and if the indoles, once formed, are not perhaps decomposed at differing rates by the strongly acid medium, with a consequent reversal of the true proportions, then cyclisation *ortho* to the nitro-group is preferred. That this was indeed so was proved by taking a mixture of known proportions of 4- and 6-nitro-2 : 3-diphenylindoles, submitting it to the conditions used in the Fischer synthesis, and analysing the resulting mixture. The result (see below) also proves that differing solubilities of the two indoles in the reaction medium cannot account for the ratio observed, but rather that allowance for solubilities increases the predominance of 4- over 6-nitro-2 : 3-diphenylindole.

In view of these results we examined the cyclisation of benzyl methyl ketone *m*-nitrophenylhydrazone. The reaction appears to be complex. By adsorption on alumina we were able to isolate 4-nitro-3-phenyl-2-methylindole, which accounted for 60% of the cyclisation mixture, but failed to resolve the remainder of the product. Crystallisation of the cyclisation mixture likewise furnished the pure major component but was equally unsuccessful in resolving the more soluble material. Since subsequent oxidation of the major product led without difficulty to 6-nitro-2-acetamidobenzophenone, whereas the minor fraction gave only an intractable gum, it seems possible that some *Bz*-nitro-2-benzylindoles were formed, giving unstable oxidation products. This result is interesting since benzyl methyl ketone phenylhydrazone is said to give 3-phenyl-2-methylindole (though this structure does not appear to have been proved) when cyclised with zinc chloride or alcoholic hydrochloric acid (Trenkler, *Annalen*, 1888, **248**, 106). Despite the complication, however, it is clear that cyclisation *ortho* to the nitro-group is again favoured.

The significance of these results will not be clear until our knowledge of the mechanism of the Fischer synthesis becomes more certain. Since the most satisfactory mechanism proposed so far (Robinson and Robinson, *J.*, 1918, **113**, 639; see also Carlin and Fisher, *J. Amer. Chem. Soc.*, 1948, **70**, 3421) treats Fischer's reaction as a particular case of the *ortho*-benzidine rearrangement, recent views on the transition states involved in the benzidine rearrangement (see, for example, Dewar, "The Electronic Theory of Organic Chemistry," 1949, p. 233) may also be applicable. We are examining further examples of the Fischer synthesis, and also the Claisen rearrangement (Tarbell, "Organic Reactions," vol. 2, New York, 1944) which is in many ways analogous to it.

Fennel and Plant (*loc. cit.*) were unable to cyclise deoxybenzoin *o*-nitrophenylhydrazone, but we have found that benzyl methyl ketone *o*-nitrophenylhydrazone readily gives 7-nitro-3-phenyl-2-methylindole. Oxidation in the usual way converted this in good yield into 3-nitro-2-acetamidobenzophenone.

The oxidation of suitable indole derivatives is obviously a practicable method of preparing nitro-2-aminobenzophenones. The high yields promise to make these reactions suitable for studies of the mechanism of indole oxidations.

Experimental.

M. p.s are uncorrected.

Nitrophenylhydrazones.—Methyl *n*-propyl ketone *o*-, m. p. 52—53°, *m*-, m. p. 51—53°, and *p*-nitrophenylhydrazone, m. p. 111—112°, resulted in yields of 77%, 69%, and 86%, respectively, when the ketone and hydrazine were heated in equivalent quantities for 1 hour at 95°, and the product was crystallised from alcohol. By the same method, benzyl methyl ketone *o*-, m. p. 102—103° (orange needles), and *m*-nitrophenylhydrazone, m. p. 103—105°, were formed in 84% and 55% yield, respectively. The corresponding *m*- and *p*-derivatives of phenyl benzyl ketone were obtained in 74% and 93% yield by the method of Fennel and Plant (*loc. cit.*).

5- and 7-Nitro-2-methyl-3-ethylindole.—The substantially pure compounds were recovered in 45% and 27% yield (based on the parent nitroanilines) when the appropriate hydrazones were heated with 10 volumes of fuming hydrochloric acid (*d* 1·19) for 4 hours at 95°, and the products washed with concentrated hydrochloric acid. *5-Nitro-2-methyl-3-ethylindole* separated from ethanol in brownish-orange leaflets, m. p. 191—192° (Found: C, 64·9; H, 5·8. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9%), and the *7-nitro*-derivative formed long scarlet needles, m. p. 135—136°, from the same solvent (Found: C, 64·2; H, 6·1%). Both compounds were unresolved by passage over an alumina column.

4- and 6-Nitro-2-methyl-3-ethylindoles.—Cyclisation of methyl *n*-propyl ketone *m*-nitrophenylhydrazone in a similar way gave 33% of mixed indoles. Adsorption of a filtered solution of the mixture (10 g.) in benzene (1 l.) on a column identical with that described in Part I (*loc. cit.*), and development with more benzene, led to separation into an upper crimson and a lower scarlet band. Elution of the latter (2·27 g.)

with benzene, and crystallisation from ethanol, provided *4-nitro-2-methyl-3-ethylindole* in scarlet rectangular prisms, m. p. 163—164° (Found: C, 64·1; H, 6·0%), whilst application of benzene–pyridine (10 : 1) removed the upper band (7·48 g.) consisting of the *6-nitro*-isomer, which separated from ethanol in brownish-orange prisms, m. p. 170—171° (Found: C, 64·9; H, 6·3%). A small intermediate fraction was not further investigated. Crystallisation of the original mixture (5 g.) from ethanol provided crude 6-nitro-2-methyl-3-ethylindole (2·07 g.), m. p. 166—165°, but the mother-liquor deposited a mixture when concentrated.

3-Nitro-2-aminopropiophenone.—7-Nitro-2-methyl-3-ethylindole (2·45 g.) in acetic acid (20 c.c.) was treated gradually with chromic anhydride (2·1 g.) in water (5 c.c.), the temperature being kept below 30°. After 2 hours the mixture was diluted with water and extracted with chloroform. Removal of the solvent after drying (Na_2CO_3) left a sticky solid (1·99 g.), crystallisation of which from alcohol gave 3-nitro-2-acetamidopropiophenone (0·60 g.), m. p. 107—108° (Found: C, 55·9; H, 5·1. Calc. for $C_{11}H_{12}O_4N_2$: C, 55·9; H, 5·1%). Hydrolysis (Keneford and Simpson, *loc. cit.*) gave 3-nitro-2-amino-propiophenone (0·37 g.), which separated from dilute ethanol in fine yellow needles, m. p. 87—88° (Found: C, 55·7; H, 5·2. Calc. for $C_9H_{10}O_3N_2$: C, 55·7; H, 5·2%).

5-Nitro-2-aminopropiophenone.—5-Nitro-2-methyl-3-ethylindole (2·4 g.) in acetic acid (20 c.c.) was treated likewise with chromic anhydride (2·04 g.) in water (5 c.c.). Worked up as above, the reaction mixture gave a sticky solid which crystallised from ethanol in pale yellow needles (0·65 g.), m. p. 165—168°. Recrystallisation from the same solvent gave the pure *product*, m. p. 171—172° (Found: C, 55·2; H, 5·3; N, 11·1. $C_{11}H_{12}O_4N_2$ requires C, 55·9; H, 5·1; N, 11·9. $C_{11}H_{14}O_4N_2$ requires C, 55·5; H, 5·9; N, 11·7. $C_{13}H_{14}O_3N_2$ requires C, 55·7; H, 5·75; N, 10·0%). This substance (0·65 g.), which depressed the m. p. of 5-nitro-2-acetamidopropiophenone (m. p. 145—145·5°; Keneford and Simpson, *loc. cit.*), was converted by boiling hydrochloric acid (5*N*.) into 5-nitro-2-aminopropiophenone, m. p. 130—131° (Found: C, 55·6; H, 5·3%), alone and mixed with an authentic specimen.

6-Nitro-2-aminopropiophenone.—In a similar way 4-nitro-2-methyl-3-ethylindole (0·3 g.) provided 0·6 g. of once crystallised (methanol) *6-nitro-2-acetamidopropiophenone* (m. p. 154—155°), which, when pure, formed buff needles, m. p. 156—157° (Found: C, 55·7; H, 5·7%). Hydrolysis with boiling hydrochloric acid (5*N*.) for ½ hour, followed by basification with aqueous ammonia, gave the *amine* (0·03 g.), which crystallised from hot water in fine orange needles, m. p. 77—78° (Found: C, 56·7; H, 5·6%).

4-Nitro-2-aminopropiophenone.—Prepared similarly from 6-nitro-2-methyl-3-ethylindole (2 g.), the *acetamido*-compound (0·37 g.; m. p. 129—131°) crystallised from ethanol in cream-coloured needles, m. p. 135—136° (Found: C, 56·2; H, 4·85%). Hydrolysis as above provided *4-nitro-2-amino-propiophenone* (0·28 g.), which separated from dilute ethanol in orange-yellow leaflets, m. p. 129—130° (Found: C, 56·2; H, 5·4%).

The amine (0·35 g.) in acetic acid (2 c.c.) and sulphuric acid (1 c.c. of 30*N*.) was diazotised at 0° with powdered sodium nitrite (0·18 g.), and the solution was diluted with ice-water (20 c.c.) and treated with hypophosphorous acid (10 c.c. of 30%). After 24 hours at 0° the mixture was made alkaline with aqueous sodium hydroxide and extracted with ether. The dried (Na_2CO_3) extract provided crude *p*-nitro-propiophenone (0·27 g.; m. p. 85—88°), which was reduced for 1 hour at 95° with tin (0·3 g.) and concentrated hydrochloric acid (2 c.c.). Extraction of the basified mixture with ether removed the crude amine (0·18 g.), which crystallised from dilute ethanol in feathery needles (0·12 g.), m. p. 139—140° (Chattaway, *J.*, 1904, **85**, 392, gives m. p. 142°). Treatment with acetic anhydride (2 c.c.) for 1 hour at 95° gave *p*-acetamidopropiophenone (0·11 g.), m. p. 171—172° (Chattaway, *loc. cit.*, gives m. p. 175°) after crystallisation from dilute ethanol (Found: C, 69·1; H, 6·9. Calc. for $C_{11}H_{13}O_2N$: C, 69·1; H, 6·85%).

Bz-Nitro-2 : 3-diphenylindoles.—5-Nitro-, m. p. 198—200°, and a mixture of 4- and 6-nitro-2 : 3-diphenylindoles, were obtained from the appropriate hydrazones (40 g.) in 60% and 69% yields, by boiling with acetic acid and concentrated hydrochloric acid (400 c.c. of each) under reflux for 16 hours. In the former case the omission of acetic acid caused extensive hydrolysis, with the formation of tarry material.

Crystallisation of the crude mixture of 4- and 6-nitro-2 : 3-diphenylindoles (25 g.) from ethanol (750 c.c.) provided the almost pure 6-nitro-compound (5·3 g.; m. p. 225—227°). Concentration of the mother-liquor to one-third of its volume gave the impure 4-nitro-2 : 3-diphenylindole, which after crystallisation from benzene melted at 204—205° (8·4 g.).

The alcoholic filtrate (150 c.c.) from the crystallisation of the crude mixed isomers (5 g.) was evaporated to dryness after removal of the slightly impure higher-melting product (1·34 g.; m. p. 225—227°), and the residue dissolved in benzene (800 c.c.). Chromatographic separation of the contents of the solution as in previous cases, using benzene as eluent, gave first 4-nitro-2 : 3-diphenylindole (3·32 g.; m. p. 202—204°) (elution was very slow) and then, by application of acetone, 6-nitro-2 : 3-diphenylindole (0·22 g.; m. p. 227—228°), of which the total yield was therefore 1·56 g. The 4-nitro-derivative separated from benzene in clusters of orange-yellow needles, m. p. 205—206° (Found: C, 76·7; H, 4·5. Calc. for $C_{20}H_{14}O_2N_2$: C, 76·4; H, 4·5%).

A mixture of pure 4- and 6-nitro-2 : 3-diphenylindole (0·2 g. of each) was boiled under reflux for 24 hours with acetic and concentrated hydrochloric acids (10 c.c. of each), and the residue after evaporation subjected to chromatographic analysis as above. Recovery of the indoles was quantitative, with no evidence of decomposition. In a further experiment, the crystalline material (0·36 g.) from the cooled cyclisation medium was resolved chromatographically, giving 4-nitro- (0·16 g.) and 6-nitro-2 : 3-diphenylindole (0·2 g.).

4-Nitro-2-aminobenzophenone.—A suspension of finely powdered 6-nitro-2 : 3-diphenylindole (5·3 g.) in glacial acetic acid (200 c.c.) was treated gradually with chromic anhydride (3·2 g.) in water (5 c.c.), and stirred until a clear solution was formed. After 12 hours at room temperature the mixture was diluted with an equal volume of water, and the practically pure product (4·07 g.; 70%) collected. *4-Nitro-2-benzamidobenzophenone* separated from ethanol in lemon-yellow needles, m. p. 192—193° (Found: C, 68·55; H, 3·9. $C_{20}H_{14}O_4N_2$,0·33 H_2O requires C, 68·2; H, 4·2%). This compound (4·07 g.) was boiled under reflux for 4 hours with acetic and concentrated hydrochloric acids (200 c.c. of each), and the clear

solution was basified with aqueous ammonia, giving *6-nitro-2-aminobenzophenone* (3·0 g.), which crystallised from dilute ethanol in small yellow needles, m. p. 172—173° (Found: C, 66·4; H, 4·2. $C_{13}H_{10}O_3N_2$ requires C, 64·5; H, 4·2%).

The amine (0·3 g.) in acetic acid (2 c.c.) and sulphuric acid (1 c.c. of 30 N.) was diazotised at 0° with powdered sodium nitrite (0·1 g.), and the diluted solution (10 c.c. of iced water) treated with hypophosphorous acid (3 c.c. of 30%). After 12 hours at 0°, the mixture was basified and extracted with ether, giving a product which on crystallisation from ethanol provided *p*-nitrobenzophenone (0·22 g.), m. p. 130—131° (Basler, *Ber.*, 1883, **16**, 2717, gives m. p. 136°). Reduction of the compound (0·1 g.) with stannous chloride (0·3 g.) and concentrated hydrochloric acid (2 c.c.) for 1 hour at 95°, gave 0·06 g. of once crystallised *p*-aminobenzophenone, m. p. 122—123° (Doebner, *Annalen*, 1881, **210**, 268, gives m. p. 124°), showing a large mixed m. p. depression with authentic *o*-aminobenzophenone (m. p. 105—106°, Hewett *et al.*, *J.*, 1948, 292).

5-Nitro-2-aminobenzophenone.—5-Nitro-2 : 3-diphenylindole (6·9 g.) was oxidised in a similar way, giving the *benzamido*-derivative (6·97 g., 91%), m. p. 196—197°. Recrystallisation from ethanol gave small colourless needles, m. p. 197—198° (Found: C, 68·2; H, 5·3. $C_{26}H_{18}O_4N_2,0{\cdot}33H_2O$ requires C, 68·2; H, 4·2%). Hydrolysis as above gave the amine (4·6 g.), m. p. 160—161° (Ullmann and Maillet, *loc. cit.*, give m. p. 161·5°).

6-Nitro-2-aminobenzophenone.—Similar treatment of 4-nitro-2 : 3-diphenylindole (7·4 g.) provided the *benzamido*-compound (8·1 g., 97%), m. p. 117—119°, which formed small colourless leaflets, m. p. 123—124°, from ethanol (Found: C, 68·9; H, 4·5. $C_{26}H_{18}O_4N_2,0{\cdot}33H_2O$ requires C, 68·2; H, 4·2%). Hydrolysis of this compound (8·1 g.) in the usual way led to *6-nitro-2-aminobenzophenone*, forming yellow leaflets, m. p. 172—173°, after crystallisation from dilute ethanol (Found: C, 64·1; H, 4·2%). Deamination of this compound as before gave *o*-nitrobenzophenone, m. p. 100—102°, forming on reduction *o*-aminobenzophenone, m. p. 105—106°, alone and mixed with an authentic specimen.

4-Nitro-2-methyl-3-phenylindole (see below) (11·6 g.) in acetic acid (200 c.c.) was oxidised in the usual way with chromic anhydride (8·1 g.) in water (10 c.c.). Worked up as before, the once crystallised product (7·1 g.; m. p. 156—157°) on further crystallisation from alcohol gave colourless hexagonal tablets of *6-nitro-2-acetamidobenzophenone*, m. p. 158—159° (Found: C, 65·2; H, 4·2. $C_{15}H_{12}O_4N_2$ requires C, 63·4; H, 4·3%). Hydrolysis of the compound (0·2 g.) with concentrated hydrochloric acid (2 c.c.), water (2 c.c.), and ethanol (5 c.c.), followed by treatment with aqueous ammonia, gave 6-nitro-2-aminobenzophenone (0·12 g.), identical with that described above.

Ba-*Nitro-3-phenyl-2-methylindoles.*—Methyl benzyl ketone *o*-nitrophenylhydrazone (6·3 g.) was heated under reflux for 2 hours with acetic and concentrated hydrochloric acids (63 c.c. of each), giving *7-nitro-3-phenyl-2-methylindole* (51%), which crystallised from ethanol in small bright orange needles, m. p. 158—159° (Found: C, 71·3; H, 4·8. $C_{15}H_{12}O_2N_2$ requires C, 71·4; H, 4·8%).

Under the conditions used for the 2 : 3-diphenylindoles, benzyl methyl *m*-nitrophenylhydrazone gave 32% (based on *m*-nitroaniline) of mixed indoles. Adsorption of the mixture (5 g.) from benzene (1 l.) on alumina in the usual way led to separation into an upper orange and a lower canary-yellow band. The latter, on elution with benzene, proved to contain *4-nitro-3-phenyl-2-methylindole* (3 g.) crystallising from ethanol in orange rhombs, m. p. 247—248° (Found: C, 70·5; H, 4·6. $C_{15}H_{12}O_2N_2$ requires C, 71·4; H, 4·8%). Application of benzene–pyridine (10 : 1) furnished the remaining material, m. p. 181—183°, which appeared to be homogeneous but showed evidence of further resolution on a fresh column. Crystallisation of the crude Fischer product (24 g.) from ethanol (800 c.c.) readily provided 4-nitro-3-phenyl-2-methylindole (11·6 g.), m. p. 243—244°, but the other much more soluble material was heterogeneous. The 4-nitro-compound was oxidised as already described, but similar treatment of the lower-melting fraction gave material which could not be crystallised.

3-Nitro-2-aminobenzophenone.—7-Nitro-3-phenyl-2-methylindole (1·5 g.) in acetic acid (50 c.c.) was treated with chromic anhydride (1·1 g.) in water (2 c.c.), and set aside overnight. The diluted solution was extracted with chloroform, and the extract washed, dried (Na_2CO_3), and concentrated. The residue (1·9 g.), when crystallised from ethanol, gave *3-nitro-2-acetamidobenzophenone* (1·5 g., 89%), which formed cream-coloured plates, m. p. 174—175° (Found: C, 63·0; H, 3·9%). Hydrolysis of this compound (0·13 g.) for 1 hour at 95°, with concentrated hydrochloric acid (2 c.c.), water (2 c.c.), and alcohol (5 c.c.), followed by basification with aqueous ammonia, gave the *amine* (0·1 g.), crystallising from dilute ethanol in bright yellow leaflets, m. p. 99—100° (Found: C, 65·0; H, 4·0%).

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312. *Synthetic Analgesics. Part X. Tertiary Carbinols and Derivatives from Mannich Bases.*

By A. L. Morrison and H. Rinderknecht.

By the action of Grignard reagents on Mannich bases derived from acetophenone, *cyclo*hexanone, and 1-tetralone, tertiary carbinols have been made. The acyl derivatives of these carbinols have only slight analgesic activity.

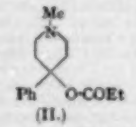
Syntheses of 6-phenyl-3-methyloctahydro-5 : 6-benz-1 : 3-oxazine and 6 : 6-diphenyl-3-methyltetrahydro-1 : 3-oxazine are described.

Some of the compounds have marked spasmolytic action.

The high analgesic potencies of 6-dimethylamino-4 : 4-diphenylheptan-3-one (amidone) (I) and 4-propionoxy-4-phenyl-1-methylpiperidine (II) have now been well established (Report No. PB-981, U.S.A. Office of the Publication Board, Department of Commerce; Foster and Carman, *J. Pharm. Exp. Ther.*, 1947, **91**, 195). The possibility that a compound such as dimethyl-3-propionoxy-3 : 3-diphenylpropylamine (III; R = R′ = Me, R″ = EtCO), in which are combined features of both these potent analgesics, might also possess considerable activity, was considered by us some time ago. The carbinol (III; R = R′ = Me, R″ = H) was readily prepared by the action of phenylmagnesium bromide on the Mannich base made from acetophenone and dimethylamine.

$Ph_2C(COEt)\cdot CH_2\cdot CHMe\cdot NMe_2$
(I.)

$Ph_2C(OR'')\cdot CH_2\cdot CH_2\cdot NRR'$
(III.)

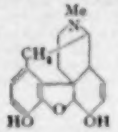


(II.)

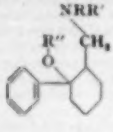
Independently of our work, similar experiments have been reported recently in America (Becker, Ananenko, Glenwood, and Miller, *Fed. Proc.*, 1946, **5**, 163; Ruddy and Buckley, 110th Meeting Amer. Chem. Soc., 14K; Report No. PB-981, U.S.A. Office of the Publication Board, Department of Commerce, p. 38), in Germany (Hoechst Nos. 10,210 and 10,214; I.G. Farbenind., F.P. 890,633/1942), and in England (Winthrop Chemical Co. Inc., B.P. Appl. 2255/47; Adamson, *J.*, 1949, S 144).

We now wish to report the preparation of a number of compounds in this series, and their acyl and other derivatives, details of which will be found in the Experimental section.

We also considered that acyl derivatives of the carbinols (V and VI; R″ = H), prepared by the action of aryl- and alkyl-magnesium halides on Mannich bases derived from *cyclo*hexanone and 1-tetralone would be of interest as they bear some structural relationship to morphine (IV).



(IV.)



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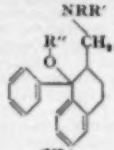


(VI.)

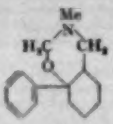
Since the completion of this work, Lee, Ziering, Berger, and Heineman ("Jubilee Volume Emil Barell," 1946, p. 264) have reported the preparation of a few representatives of this series.

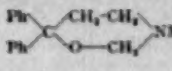
We have found generally that the yields of *tert.*-alcohols formed by the action of Grignard reagents on Mannich bases are not good but can usually be improved if the finely powdered hydrochloride is added in portions to a well-cooled, stirred solution of the Grignard reagent in ether.

In all the publications cited mention is made, and in some cases details are given, of the dehydration of such tertiary carbinols to the unsaturated compounds, and of the subsequent hydrogenation to give the propane derivatives. We have also dehydrated the tertiary alcohols by heating them for about 48 hours with 98% formic acid and hydrogenated the resultant unsaturated amines.

Finally, in an attempt to simulate the piperidine ring of morphine, 1-phenyl-2-methylaminomethyl*cyclo*hexan-1-ol was treated with formaldehyde to give 6-phenyl-3-methyloctahydro-

5 : 6-benz-1 : 3-oxazine (VII). In the same manner 6 : 6-diphenyl-3-methyltetrahydro-1 : 3-oxazine (VIII) was made from 3-methylamino-1 : 1-diphenylpropan-1-ol.

(VII.) 

 (VIII.)

None of the compounds reported in this communication possessed analgesic activity greater than that of pethidine. Some, however, exhibited considerable antihistamine and spasmolytic properties and the results of this pharmacological investigation will be reported elsewhere.

Experimental.

3-Dimethylamino-1 : 1-diphenyl-1-propanol (III; R = R′ = Me, R″ = H).—ω-Dimethylaminopropiophenone hydrochloride (19·6 g.) was added in small portions, with cooling and stirring, to an ethereal solution of phenylmagnesium bromide prepared from magnesium (4·9 g.) and bromobenzene (32 g.). The mixture was left for 16 hours at room temperature and then decomposed by stirring with excess of ammonium chloride solution. The product was extracted with benzene and, after removal of the benzene, the solid residue was recrystallised from light petroleum (b. p. 80—100°) to give the pure tertiary alcohol, m. p. 164—165° (11·6 g., 55%) (Found: C, 79·4; H, 8·1; N, 5·6. Calc. for $C_{17}H_{21}ON$: C, 80·0; H, 8·2; N, 5·5%).

When the above base was warmed with acetic anhydride for a short time and then left at room temperature overnight and the excess of acetic anhydride then distilled off, a product was obtained, practically insoluble in water and soluble in ether. It proved to be the *acetate*, m. p. 115—118° when recrystallised from light petroleum (b. p. 80—100°) (Found: C, 70·5; H, 7·0; N, 3·8. $C_{19}H_{23}O_2N$ requires C, 70·6; H, 7·0; N, 3·9%), of the *1-acetoxy-base*; the latter, crystallised from light petroleum (b. p. 60—80°), had m. p. 111—114° (Found: C, 77·2; H, 7·9; N, 4·6. $C_{19}H_{23}O_2N$ requires C, 76·8; H, 7·7; N, 4·7%).

3-Dimethylamino-1-propionoxy-1 : 1-diphenylpropane propionate (III; R = R′ = Me, R″ = EtCO), prepared similarly, had m. p. 94—96° when recrystallised from light petroleum (b. p. 40—60°) (Found: C, 71·7; H, 8·2; N, 4·1. $C_{23}H_{31}O_4N$ requires C, 71·7; H, 8·0; N, 3·6%).

The base (III; R = R′ = Me, R″ = H) (5 g.) was added to a solution of nicotinyl chloride (5·5 g.) in dry pyridine. After being kept overnight at room temperature, the pyridine was distilled off at 12 mm. The residue was dissolved in benzene and washed with a dilute solution of sodium carbonate and then water. Concentration of the benzene solution left an oily product which became partly crystalline *in vacuo* in presence of concentrated sulphuric acid. Recrystallisation from light petroleum (b. p. 60—80°) gave the pure *1-nicotinate*, m. p. 92—94° (Found: C, 76·9; H, 6·7; N, 7·15. $C_{23}H_{24}O_2N_2$ requires C, 76·7; H, 6·7; N, 7·8%).

3-Dimethylamino-1 : 1-diphenylprop-1-ene.—Refluxing a solution of (III; R = R′ = Me, R″ = H) in formic acid for 48 hours yielded the unsaturated base with properties described by Adamson (*loc. cit.*). It gave a *picrate*, m. p. 159—160° (Found: C, 59·3; H, 4·8; N, 12·4. $C_{23}H_{22}O_7N_4$ requires C, 59·2; H, 4·7; N, 12·0%). The *picrate* of 3-dimethylamino-1 : 1-diphenylpropane (Found: C, 59·3; H, 4·9; N, 12·3. $C_{23}H_{24}O_7N_4$ requires C, 59·0; H, 5·1; N, 12·0%) also melted at 159° but a mixture of the two picrates melted at 134—140°.

3-Dimethylamino-1-phenyl-1-o-tolylpropan-1-ol.—This *base* was prepared in a manner as described for (III; R = R′ = Me, R″ = H), using o-tolylmagnesium bromide, and obtained as a solid, m. p. 131—134°, from acetone (Found: C, 80·4; H, 8·8; N, 4·7. $C_{18}H_{23}ON$ requires C, 80·3; H, 8·6; N, 5·2%). Heating it with propionic anhydride gave *3-dimethylamino-1-propionoxy-1-phenyl-1-o-tolylpropane propionate* m. p. 81—83° [from light petroleum ether (b. p. 40—60°)] (Found: C, 72·8; H, 8·1; N, 3·8. $C_{24}H_{31}O_4N$ requires C, 72·2; H, 8·3; N, 3·5%).

ω-Benzylmethylaminopropiophenone Hydrochloride.—Benzylmethylamine hydrochloride (17·5 g.), acetophenone (14 g.), and paraformaldehyde (7 g.) in ethanol (75 ml.) were heated on the steam-bath under reflux for 20 minutes. The clear solution obtained was concentrated to about half its volume and on cooling the *hydrochloride* crystallised, having m. p. 196—198° (9·6 g.) (Found: Cl′, 12·2. $C_{17}H_{20}ONCl$ requires Cl′, 12·3%).

3-Benzylmethylamino-1 : 1-diphenylpropan-1-ol (III; R = Me, R′ = Ph·CH_2, R″ = H).—In the usual manner ω-benzylmethylaminopropiophenone hydrochloride (9·2 g.) was treated with phenylmagnesium bromide, prepared from bromobenzene (11 g.) and magnesium (1·7 g.), to give the tert.-*alcohol*, which distilled at 180—184°/0·2 mm. and had m. p. 100—102° (Found: C, 83·2; H, 7·7; N, 4·9. $C_{23}H_{25}ON$ requires C, 83·4; H, 7·6; N, 4·2%). The *hydrochloride*, crystallised from alcohol–ether, had m. p. 195° (Found: N, 3·9. $C_{23}H_{24}ONCl$ requires N, 3·8%).

3-Methylamino-1 : 1-diphenylpropan-1-ol (III; R = Me, R′ = R″ = H).—The above base (6·9 g.) in alcohol was hydrogenated in the presence of palladium–charcoal in the usual manner, to remove the benzyl group. The product distilled at 140—150°/0·2 mm. and was recrystallised from alcohol to give the pure alcohol, m. p. 145—147° (cf. Adamson, *loc. cit.*) (Found: C, 79·8; H, 7·9; N, 5·9. Calc. for $C_{16}H_{19}ON$: C, 79·7; H, 7·9; N, 5·8%).

6 : 6-Diphenyl-3-methyltetrahydro-1 : 3-oxazine (VIII).—A mixture of 3-methylamino-1 : 1-diphenylpropan-1-ol (1·9 g.), 40% formaldehyde solution (1·2 ml.), and potassium carbonate (1·1 g.) in alcohol (10 ml.) was shaken for 8 hours. Water was then added, the precipitated product extracted with ether, and the ethereal solution well washed with water, dried (Na_2SO_4), and concentrated. The residue

distilled at 133—135°/0·1 mm. to give the *tetrahydro*-1 : 3-*oxazine*, m. p. 83—85° (1·6 g.) (Found : C, 80·9; H, 7·6; N, 5·55; Active H, 0. $C_{11}H_{13}ON$ requires C, 80·6; H, 7·5; N, 5·5; Active H, 0%).

3-*Dimethylamino*-1-*phenyl*-1-*benzylpropan*-1-*ol*.—Treatment of α-dimethylaminopropiophenone hydrochloride (21·3 g.) with benzylmagnesium bromide, prepared from benzyl bromide (44 g.) and magnesium (6 g.) in ether, gave the tert.-*alcohol* in very poor yield. Recrystallised from light petroleum (b. p. 40—60°) it melted at 80—82° (Found : C, 80·6; H, 8·7; N, 4·85. $C_{18}H_{23}ON$ requires C, 80·3; H, 8·6; N, 5·2%).

1-*Dimethylaminomethylpropiophenone Hydrochloride*.—Propiophenone (28 g.), dimethylamine hydrochloride (9·4 g.), and paraformaldehyde (15 g.) in ethanol (100 ml.) were heated under reflux until the aldehyde went into solution. The product left after distilling off the alcohol was recrystallised from 2 : 1 ethanol–acetone, the *hydrochloride*, m. p. 152—154°, being obtained (Found : Cl′, 16·1. $C_{12}H_{18}ONCl$ requires Cl′, 15·4%).

3-*Dimethylamino*-1 : 1-*diphenyl*-2-*methylpropan*-1-*ol*.—The above Mannich base hydrochloride (3 g.) was treated with phenylmagnesium bromide, prepared from bromobenzene (4·6 g.) and magnesium (0·5 g.), to give the tert.-*alcohol* which, recrystallised from acetone, had m. p. 158—161° (Found : C, 79·8; H, 8·1; N, 5·2. $C_{18}H_{23}ON$ requires C, 80·2; H, 8·6; N, 5·2%).

1-*Phenyl*-2-*dimethylaminomethyl*cyclo*hexan*-1-*ol* (V; R = R′ = Me, R″ = H).—2-Dimethylamino-*cyclo*hexan-1-one (5 g.) and phenylmagnesium bromide, prepared from bromobenzene (10 g.) and magnesium (1·6 g.), in the usual way gave the tert.-*alcohol*, b. p. 108—111°/0·5 mm. (3·8 g., 50%) (Found : C, 76·5; H, 10·0; N, 5·7. $C_{15}H_{23}ON$ requires C, 77·2; H, 9·9; N, 6·0%). Treatment of the alcohol with acetic anhydride in the usual way gave 1-*acetoxy*-1-*phenyl*-2-*dimethylaminomethyl*cyclo*hexane* (V; R = R′ = Me, R″ = Ac), a low-melting solid, b. p. 130—131°/0·8 mm. (Found : C, 74·4; H, 9·25; N, 4·8. $C_{17}H_{25}O_2N$ requires C, 74·2; H, 9·1; N, 5·1%). 1-*Propionoxy*-1-*phenyl*-2-*dimethylaminomethyl*cyclo*hexane* (V; R = R′ = Me, R″ = EtCO) was also a low-melting solid, b. p. 123—125°/0·4 mm. (Found : C, 74·35; H, 9·35; N, 4·4. $C_{18}H_{27}O_2N$ requires C, 74·75; H, 9·35; N, 4·9%).

1-*Benzoyloxy*-1-*phenyl*-2-*dimethylaminomethyl*cyclo*hexane* (V; R = R′ = Me, R″ = Bz).—Benzoylation of the alcohol (5 g.) was carried out by heating it in acetone (25 ml.) with benzoyl chloride (3·3 g.) under reflux for 1 hour. The acetone was distilled off and water added. The aqueous solution was made alkaline and extracted with ether, and the ethereal solution dried and concentrated. Distillation of the residue gave the *ester* which, recrystallised from alcohol, had m. p. 108—111° (Found : C, 78·1; H, 7·8; N, 4·0. $C_{22}H_{27}O_2N$ requires C, 78·35; H, 8·0; N, 4·15%).

1-*Phenyl*-2-*dimethylaminomethyl*cyclo*hexa*-1- *or* -6-*ene*.—The above alcohol (4 g.) was dehydrated by heating it with 98% formic acid (20 ml.) at 140° for 48 hours to give a product, the *picrate* of which had m. p. 140—141° (from alcohol) (Found : C, 56·75; H, 5·4. $C_{21}H_{24}O_7N_4$ requires C, 56·8; H, 5·4%).

1-*Phenyl*-2-*dimethylaminomethyl*cyclo*hexane*.—Hydrogenation of the above unsaturated base (1 g.) in alcohol (20 ml.) in presence of palladium–charcoal gave the saturated *base*, b. p. 147—149°/13 mm. (Found : C, 82·7; H, 10·5. $C_{15}H_{23}N$ requires C, 82·9; H, 10·6%). It formed a *picrate* m. p. 139—141° (Found : N, 12·6. $C_{21}H_{26}O_7N_4$ requires N, 12·6%). A mixture with the picrate of the starting material melted at 122—128°.

2-*Benzylmethylaminomethyl*cyclo*hexan*-1-*one Hydrochloride*.—Benzylmethylamine hydrochloride (18·2 g.), *cyclo*hexanone (14·7 g.), and paraformaldehyde (9 g.) in ethanol (75 ml.) were heated on the steam-bath under reflux for 30 minutes. The alcohol was then distilled off and the solid residue recrystallised from ethyl acetate to give the pure *hydrochloride*, m. p. 144—146° (16·6 g., 54%) (Found : Cl′, 13·2. $C_{16}H_{24}ONCl$ requires Cl′, 13·3%).

1-*Phenyl*-2-*benzylmethylaminomethyl*cyclo*hexan*-1-*ol* (V; R = Me, R′ = CH_2Ph, R″ = H).—Reaction of the above Mannich base hydrochloride with 2·2 moles of phenylmagnesium bromide in the usual manner gave a 29% yield of the *alcohol*, which was obtained as a low-melting solid with b. p. 170—173°/0·6 mm. (Found : N, 4·5. $C_{21}H_{27}ON$ requires N, 4·6%).

1-*Phenyl*-2-*methylaminomethyl*cyclo*hexan*-1-*ol* (V; R = Me, R′ = R″ = H).—Hydrogenolysis of the benzyl group of the above compound in the usual way gave the *alcohol* as a liquid, b. p. 110—112°/0·4 mm. (Found : C, 76·4; H, 9·4; N, 6·55. $C_{14}H_{21}ON$ requires C, 76·7; H, 9·6; N, 6·4%).

6-*Phenyl*-3-*methyloctahydro*-5 : 6-*benz*-1 : 3-*oxazine* (VII).—The above alcohol (2 g.) was dissolved in ethanol (10 ml.), potassium carbonate (1·26 g.) and 40% formaldehyde solution (1·37 ml.) were added, and the mixture was shaken for 8 hours. Worked up in the normal way, the *oxazine* was obtained as a solid, m. p. 70—72°, b. p. 92—94°/0·3 mm. (Found : C, 77·9; H, 9·1; N, 6·1. $C_{15}H_{21}ON$ requires C, 77·9; H, 9·1; N, 6·1%).

1-*Phenyl*-2-*piperidinomethyl*cyclo*hexan*-1-*ol*.—2-Piperidinomethylcyclo*hexan*-1-one hydrochloride and phenylmagnesium bromide reacted in the usual manner to give a poor yield of the tert.-*alcohol* which melted at 83—85° when recrystallised from alcohol–water (Found : C, 79·2; H, 9·7; N, 4·8. $C_{18}H_{27}ON$ requires C, 79·1; H, 9·9; N, 5·1%).

6-*Methyl*-2-*dimethylaminomethyl*cyclo*hexan*-1-*one Hydrochloride*.—2-Methylcyclohexanone (11·2 g.), dimethylamine hydrochloride (9 g.), and paraformaldehyde (6 g.) in ethanol (50 ml.) were heated under reflux for 30 minutes. On concentration of the alcoholic solution the *hydrochloride* crystallised. Recrystallised from alcohol–acetone, it had m. p. 167—169° (Found : Cl′, 16·8. $C_{10}H_{20}ONCl$ requires Cl′, 17·1%).

1-*Phenyl*-6-*methyl*-2-*dimethylaminomethyl*cyclo*hexan*-1-*ol*.—Addition of the above hydrochloride (9 g.) to phenylmagnesium bromide, prepared from bromobenzene (14·8 g.) and magnesium (2·9 g.), gave a 50% yield of the tert.-*alcohol* which was obtained as a low-melting solid, b. p. 106—107°/0·2 mm. (Found : C, 77·7; H, 10·1; N, 5·4. $C_{16}H_{25}ON$ requires C, 77·8; H, 10·1; N, 5·7%).

1-*Phenyl*-2-*dimethylaminomethyl*-1 : 2 : 3 : 4-*tetrahydro*-1-*naphthol* (VI; R = R′ = Me, R″ = H).—2-Dimethylaminomethyl-1-tetralone hydrochloride and phenylmagnesium bromide (2·2 moles) gave a 56% yield of the *tetrahydronaphthol*, a colourless viscous oil, b. p. 170°/0·6 mm. (Found : C, 81·1; H, 8·2; N, 4·5. $C_{19}H_{23}ON$ requires C, 81·1; H, 8·2; N, 5·0%). Acetylation with acetic anhydride gave the 1-*acetate* as a viscous oil, b. p. 170°/0·1 mm. (Found : C, 77·9; H, 7·8; N, 4·3. $C_{21}H_{25}O_2N$ requires C, 78·0; H, 7·7; N, 4·3%).

1-*Phenyl*-2-*dimethylaminomethyl*-3 : 4-*dihydronaphthalene*.—The above tetrahydronaphthol was dehydrated by heating it in formic acid solution for 48 hours. The crude product gave a *picrate* which on recrystallisation from alcohol–acetone melted at 199—200° (Found : C, 61·15; H, 5·0; N, 11·8. $C_{31}H_{29}O_7N_5$ requires C, 61·0; H, 4·9; N, 11·4%).

1-*Phenyl*-2-*dimethylaminomethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—Hydrogenation of the crude product obtained in the previous experiment in the presence of palladium–charcoal gave an oil, the *picrate* of which, recrystallised from alcohol, melted at 183—185° (Found : N, 11·5. $C_{31}H_{33}O_7N_5$ requires N, 11·3%).

1-cyclo*Hexyl*-2-*dimethylaminomethyl*-1 : 2 : 3 : 4-*tetrahydro*-1-*naphthol Hydrochloride*.—Addition of 2-dimethylaminomethyl-1-tetralone hydrochloride to *cyclo*hexylmagnesium bromide in ether gave a small yield of product which yielded a *hydrochloride*, sparingly soluble in water, and on recrystallisation from alcohol melted at 236—237° (Found : C, 70·1; H, 9·25; N, 4·3. $C_{18}H_{28}ONCl$ requires C, 70·6; H, 9·3; N, 4·3%).

1-*Propionoxy*-1-cyclo*hexyl*-2-*dimethylaminomethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene Hydrochloride*.—The above hydrochloride was heated with propionic anhydride at 105° until it had all dissolved; the propionic anhydride was distilled off and the residue recrystallised from acetone–ether. The *hydrochloride* melted at 180° (Found : N, 3·5. $C_{23}H_{34}O_2NCl$ requires N, 3·7%).

2-*Dimethylaminomethyl*-1-*ethyl*-1 : 2 : 3 : 4-*tetrahydro*-1-*naphthol*.—Addition of 2-dimethylaminomethyl-1-tetralone hydrochloride (12 g.) to ethylmagnesium iodide (17 g. of ethyl iodide, 2·9 g. of magnesium) in ether gave a small yield of product isolated as the *hydrochloride* (4 g.), which, recrystallised from acetone–alcohol, melted at 209—210° (Found : C, 67·0; H, 9·0; N, 4·9. $C_{15}H_{26}ONCl$ requires C, 66·9; H, 8·9; N, 5·2%).

1-*Propionoxy*-2-*dimethylaminomethyl*-1-*ethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—Heating the above hydrochloride (0·5 g.) in propionic anhydride (50 ml.) at 90° until all had dissolved, distilling off some of the propionic anhydride, and cooling, yielded the *hydrochloride*, m. p. 183° (Found : C, 66·2; H, 8·6; Cl, 10·7. $C_{18}H_{28}O_2NCl$ requires C, 66·5; H, 8·6; Cl, 10·8%).

1-*Phenyl*-2-*piperidinomethyl*-1 : 2 : 3 : 4-*tetrahydro*-1-*naphthol*.—Addition of 2-piperidinomethyl-1-tetralone hydrochloride (8·9 g.) to phenylmagnesium bromide (bromobenzene, 11 g.; magnesium, 1·49 g.) in ether gave the crude *tert.*-alcohol which was isolated as the *hydrochloride*, m. p. 238—239° (decomp.). This was recrystallised from alcohol–ether and from its analysis appears to contain one mole of alcohol of crystallisation (Found : C, 71·3; H, 8·4; N, 3·6. $C_{24}H_{32}ONCl,C_2H_5\cdot OH$ requires C, 71·4; H, 8·4; N, 3·5%).

1-*Phenyl*-2-*piperidinomethyl*-3 : 4-*dihydronaphthalene*.—The base (2 g.) liberated from the above hydrochloride was dehydrated in the usual manner to give an oil (1·5 g.) which boiled at 175—180°/0·5 mm. and gave a *hydrochloride*, m. p. 189—190°, containing 1 mole of alcohol of crystallisation (Found : C, 75·0; H, 8·1; N, 4·0. $C_{24}H_{31}NCl,C_2H_5\cdot OH$ requires C, 74·7; H, 8·3; N, 3·6%). The *picrate*, crystallised from alcohol, melted at 156—158° (Found : C, 63·3; H, 4·7; N, 10·5. $C_{31}H_{32}O_7N_4$ requires C, 63·2; H, 5·3; N, 10·5%).

1-*Phenyl*-2-*piperidinomethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—The base (1·9 g.) liberated from the above hydrochloride was dissolved in glacial acetic acid (20 ml.) and hydrogenated in the presence of platinum oxide (0·1 g.) to give an oil, the *hydrochloride* (1 g.) of which melted at 277—278° after 2 recrystallisations from alcohol–ether (Found : C, 77·0; H, 8·0; N, 4·0. $C_{24}H_{34}NCl$ requires C, 77·3; H, 8·2; N, 4·1%).

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313 *The Stobbe Condensation between* meso*Benzanthrone and Ethyl Succinate.*

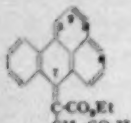
By G. R. Clemo, L. Munday, and G. A. Swan.

meso*Benzanthrone and ethyl succinate give an aldol-type condensation product. The low yield and the difficult purification of the product reduce the value of the reaction as a possible synthetic route to higher polycyclic hydrocarbons.*

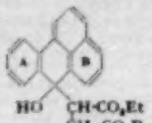
If *meso*benzanthrone reacted in the Stobbe condensation to give (I) and ultimately the corresponding propionic acid derivative, subsequent cyclisation would lead to a polycyclic derivative.

Johnson, Goldman, and Schneider's method (*J. Amer. Chem. Soc.*, 1945, **67**, 1357), in which the reaction is carried out in *tert.*-butanol, gives only very low yields of an impure product because of the low solubility of *meso*benzanthrone in the boiling solvent. However, reaction in boiling toluene, with finely divided potassium *tert.*-butoxide, affords a 16% yield of an acid. Analyses of this acid and of its methyl ester suggest that it is β-carbethoxy-β-(7-hydroxybenzanthren-7-yl)propionic acid (II), the methyl ester being (III). It is known that, in the Stobbe reaction, benzophenone and fluorenone yield substituted itaconic acids (cf. I) (Stobbe, *Annalen*, 1899, **308**, 89; Stobbe and Gollücke, *Ber.*, 1906, **39**, 1066), although an aldol (cf. II) is presumably an intermediate. For elimination of the hydroxyl group and the hydrogen atom of the α-CH group to form the ethylenic bond, the attached groups must become coplanar. A model suggests that this is improbable in the present case as the carbethoxy-group and the

hydrogen atoms at positions 6 and 8 come into too close proximity. In the case of benzophenone, the two phenyl groups are free to rotate and so do not interfere.

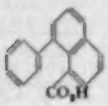


(I.)

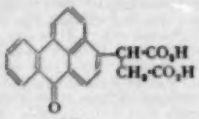


(II; R = H.)
(III; R = Me.)

(IV.)



(V.)



(VI.)

In G.P. 499,320 and 501,282 (*Chem. Zentr.*, 1930, II, 2697, 2696) it is claimed that *meso*benzanthrone can be condensed in position 4 with compounds containing a reactive methylene group. This does not seem to have been proved, however, and under the very mild reaction conditions used therein it would appear unlikely that two hydrogen atoms would be eliminated to give compounds such as (VI).

A possible, but less likely, interpretation of the analytical figures is that the action of potassium *tert.*-butoxide splits *meso*benzanthrone to (IV) or (V), as it is known that non-enolisable ketones may undergo such fission (Swan, *J.*, 1948, 1408), and that reaction with the succinic ester then ensues. However, when *meso*benzanthrone in toluene was treated with potassium *tert.*-butoxide, only a trace of acidic product was obtained: in addition to unchanged *meso*benzanthrone, 4 : 4′-dibenzanthronyl was isolated (the latter was also produced during the Stobbe condensation).

Experimental.

β-Carbathoxy-β-(7-hydroxybenzanthren-7-yl)propionic Acid (II).—To potassium (1·2 g., 0·03 mol.), powdered under toluene (70 c.c.), *tert.*-butanol (2·8 c.c., 0·03 mol.) was added slowly, agitation being continued for 4 hours and the mixture kept overnight at room temperature. *meso*Benzanthrone (6·0 g., 0·026 mol.) and ethyl succinate (7·8 g., 0·045 mol.) were added, and the mixture was stirred and heated under reflux for 6 hours in a current of nitrogen. The solution darkened rapidly. It was then cooled and washed with water (3 × 50 c.c.). The deep-brown aqueous layer was washed with toluene, filtered, and acidified. The resulting pale brown solid (1·55 g.) was dried in a vacuum-desiccator and recrystallised from benzene–light petroleum, giving the *acid* (II) as a fawn-coloured, micro-crystalline solid, m. p. 151—152° (decomp.) after sintering and darkening at 100° (Found: C, 73·55; H, 5·1. $C_{25}H_{20}O_5$ requires C, 73·4; H, 5·3%).

A solution of the acid (0·2 g.) in ethyl acetate (20 c.c.) was treated with one of diazomethane (0·12 g.) in ether (10 c.c.), and the mixture was set aside overnight. The solvents were removed (reduced pressure). The black, tarry residue was extracted with boiling benzene and the solution diluted with light petroleum (b. p. 60—80°). The resulting light-brown solid recrystallised from benzene–light petroleum (charcoal), affording the *methyl* ester (III) as a buff-coloured powder, m. p. 142—146° (decomp.) (Found: C, 74·0; H, 5·2. $C_{26}H_{22}O_5$ requires C, 73·85; H, 5·6%).

Action of Potassium tert.*-Butoxide on* meso*Benzanthrone.*—*meso*Benzanthrone (3 g.) in dry toluene (38 c.c.) was heated under reflux for 8 hours with potassium *tert.*-butoxide (4·4 g.), with the addition of water (0·23 g.), cooled, washed with sodium hydroxide solution and water, dried, and concentrated. On cooling, a yellowish-brown powder separated; this was recrystallised from toluene, giving 4 : 4′-dibenzanthronyl, m. p. 310—315° (lit., 320—321°).

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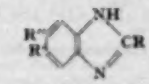
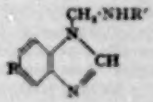
314. *Structure and Antimalarial Activity. Part IV. Benziminazoles and Mercaptodihydroglyoxalines.*

By A. T. James and E. E. Turner.

Various derivatives of benziminazole substituted in positions 1, 2, 4, 5, and 6 have been prepared and slight antimalarial activity has been demonstrated in certain of them. A small number of 4 : 5-dihydroglyoxalines substituted in position 1 or 2 has been prepared and slight activity has been found in one or two cases.

Benziminazoles bearing aliphatic chains in position 2 have been shown by Clemo and Swan (*J.*, 1944, 274) and by Turner and Hall (*J.*, 1948, 1909) to be inactive against *Plasmodium relictum* and *Plasmodium gallinaceum* in chicks. This result was confirmed when 5(or 6)-chloro-6(or 5)-methoxy-2-methylbenziminazole (I; R = Me, R′ = Cl, R″ = MeO) and 5-chloro-2-pentadecylbenziminazole (I; R = $C_{15}H_{31}$, R′ = Cl, R″ = H) were found to be inactive. Introduction of a carboxyl group at position 2 to give β-(5-chlorobenziminazol-2-yl)propionic acid (I; R = $CH_2{\cdot}CH_2{\cdot}CO_2H$, R′ = Cl, R″ = H) failed to induce activity, as did similar introduction of a hydroxymethyl group.

(I.) 

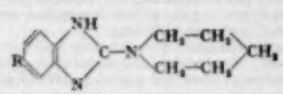
 (II.)

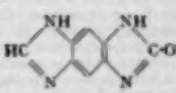
Woolley (*J. Biol. Chem.*, 1944, **152**, 225) has shown that benziminazole and 4-nitro- and 4-amino-benziminazole inhibited the growth of certain yeasts and bacteria, the inhibition being reversed by the purines adenine and guanine.

The similarity of the structures of these purines and 4- and 5-amino- and -nitro-benziminazoles suggested that these compounds might display some activity against avian malaria. However, 5-amino- (I; R = R″ = H, R′ = NH_2), 5-nitro-2-mercapto- (I; R = SH, R′ = NO_2, R″ = H), and 5-amino-2-mercaptobenziminazole (I; R = SH, R′ = NH_2, R″ = H) all proved to be inactive.

Slight antimalarial activity was found in the following benziminazoles: 1-(2-pyridylaminomethyl)- (II; R = H, R′ = 2-pyridyl), 4-nitro-1-(2-pyridylaminomethyl)- (II; R = NO_2, R′ = 2-pyridyl), and 4-nitro-1-(2-hydroxyethylaminomethyl)-benziminazole (II; R = NO_2, R′ = $CH_2{\cdot}CH_2{\cdot}OH$).

5-Nitro-2-aminobenziminazoles were next selected for trial as they possess a cyclic guanide structure. Attempts to synthesise such compounds by the cyclisation of the appropriate *o*-aminophenylureas failed, though a variety of condensing agents including sodium propionate in propionic acid, phosphorus oxychloride, sulphuric acid, and zinc chloride was used. The most effective method for the synthesis of these compounds was that described by Kym and Ratner (*Ber.*, 1912, **45**, 3238), consisting in heating the appropriate amine with 2-chlorobenziminazole. In this way 5-nitro-2-(*p*-chloroanilino)benziminazole (I; R = *p*-Cl·$C_6H_4{\cdot}NH$, R′ = NO_2, R″ = H) and 5-nitro-2-piperidinobenziminazole (III; R = NO_2) were prepared. Both substances were soluble in alkali to give deeply coloured solutions and were tested as such since the hydrochlorides were not very soluble in water. Reduction of the nitro-group to give 5-amino-2-piperidinobenziminazole (III; R = NH_2) failed to induce any activity.

(III.) 

 (IV.)

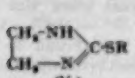
Mono-, di-, and tri-nitro-derivatives of 2-hydroxybenziminazole were readily prepared. The action of nitric acid (*d* 1·42) on 2-hydroxybenziminazole afforded 5-nitrobenziminazolone, nitration with fuming nitric acid afforded 5 : 6-dinitrobenziminazolone, and nitration with a mixture of concentrated sulphuric and nitric acids afforded 4 : 5 : 6-trinitrobenziminazolone.

The reaction between dinitrobenziminazolone and aromatic amines, reported by Kym and Ratner (*loc. cit.*) to result in the replacement of one of the nitro-groups by an amine residue, was found to be complex and to give rise, in the case of *p*-chloroaniline, to a variety of coloured products. No indication of simple replacement of one of the nitro-groups was found with

this amine. The trinitrobenziminazolone reacted violently with aliphatic and aromatic amines to give dinitro-aminobenziminazolones, the position at which the amino-group entered the benzene ring being unknown.

5-Nitrobenziminazolone proved to be inactive, 6-chloro-5-nitrobenziminazolone showed slight antimalarial activity. Slight activity was also displayed by dinitro-*p*-chloroanilinobenziminazolone, and dinitro*iso*propylaminobenziminazolone. Trinitrobenziminazolone was inactive, as was 2-hydroxyglyoxalino(4′ : 5′-5 : 6)benziminazole (IV). All these derivatives, except (IV), dissolved readily in weakly alkaline solutions to give intensely coloured solutions, and were tested as such.

A few derivatives of 2-mercapto-4 : 5-dihydroglyoxaline (V; R = H) were synthesised, but no marked antimalarial activity was displayed by any of them. 2-Mercapto-4 : 5-dihydro-



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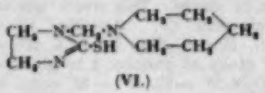
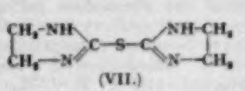


(VI.)



(VII.)

glyoxaline was slightly active, but (4 : 5-dihydroglyoxalin-2-ylthio)acetic acid (V; R = $CH_2{\cdot}CO_2H$) was inactive. Introduction of the piperidinomethyl group at the 1 position, to give 2-mercapto-1-piperidinomethyl-4 : 5-dihydroglyoxaline (VI), gave rise to slight activity. Bis-4 : 5-dihydroglyoxalin-2-yl sulphide (VII) proved inactive.

The pharmacological tests were carried out by Drs. Hawking and W. M. Perry of the National Institute for Medical Research.

Experimental.

(All m. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss, Oxford.)

2-Chloro-4-nitroanisole.—*o*-Chloroanisole (1 mol.) was nitrated in glacial acetic acid with nitric acid (2·5 mols.; *d* 1·42) by heating the mixture under reflux for 2 hours (cf. Reverdin and Eckhard, *Ber.*, 1899, **32**, 2622). On cooling, needles of 2-chloro-4-nitroanisole (52%) separated and after crystallisation from alcohol had m. p. 93—94°.

2-Chloro-4-acetamidoanisole.—2-Chloro-4-nitroanisole was reduced with iron filings and very dilute hydrochloric acid. After neutralisation with aqueous ammonia, alcohol was added and the iron, etc., were removed by filtration. The brownish product obtained after removal of the alcohol was acetylated with acetic anydride. Crystallisation from water (charcoal) gave a product, m. p. 94° (Reverdin and Eckhard, *loc. cit.*).

2-Chloro-5-nitro-4-acetamidoanisole.—Nitration of 2-chloro-4-acetamidoanisole in a mixture of concentrated sulphuric and nitric acids below 20° gave a brown crystalline product when the mixture was poured on crushed ice. Crystallisation from glacial acetic acid afforded yellow needles, m. p. 158°. Hydrolysis with concentrated hydrochloric acid gave *2-chloro-5-nitro-4-aminoanisole*, m. p. 133° after crystallisation from alcohol (Found: N, 13·6; Cl, 17·1. $C_7H_7O_3N_2Cl$ requires N, 13·8; Cl, 17·5%).

2-Chloro-5-amino-4-acetamidoanisole.—2-Chloro-5-nitro-4-acetamidoanisole was reduced in alcoholic solution with hydrogen in the presence of Raney nickel. The *base* obtained after removal of the nickel and alcohol crystallised from water as lozenges, m. p. 157° (Found: N, 13·2. $C_9H_{11}O_2N_2Cl$ requires N, 13·1%). The *hydrochloride*, m. p. 282° (decomp.), was obtained by passage of hydrogen chloride into a solution of the base in alcohol, followed by precipitation by ether (Found: C, 43·6; H, 4·8; N, 11·0. $C_9H_{12}O_2N_2Cl_2$ requires C, 43·0; H, 4·8; N, 11·2%).

5-Chloro-6-methoxy-2-methylbenziminazole.—2-Chloro-5-amino-4-acetamidoanisole was heated in propionic acid with fused sodium propionate. Neutralisation and crystallisation from alcohol gave 5-chloro-6-methoxy-2-methylbenziminazole, converted into the *hydrochloride*, m. p. 262° (Found: N, 12·0. $C_9H_{10}ON_2Cl_2$ requires N, 12·0%).

4-Chloro-2-nitropalmitoanilide.—4-Chloro-2-nitroaniline (5 g.) was heated in dry toluene with palmitoyl chloride (8 g.) for 1 hour. On evaporation of the toluene and crystallisation of the product twice from alcohol and then from acetone–light petroleum, a pale yellow crystalline *anilide* (10 g.), m. p. 76°, was obtained (Found: N, 6·5. $C_{22}H_{35}O_3N_2Cl$ requires N, 6·8%).

4-Chloro-2-aminopalmitoanilide.—4-Chloro-2-nitropalmitoanilide (7·5 g.) was reduced in alcoholic solution with hydrogen in the presence of Raney nickel. Removal of the nickel and alcohol, followed by crystallisation from aqueous alcohol, gave a crystalline *product* (4·6 g.), m. p. 103° (Found: N, 6·9. $C_{22}H_{37}ON_2Cl$ requires N, 7·4%).

5-Chloro-2-pentadecylbenziminazole.—4-Chloro-2-aminopalmitoanilide (5 g.) was heated in propionic acid with fused sodium propionate (1 g.) for 1 hour. The solution was then diluted and neutralised with 10% sodium hydroxide solution. The precipitate was crystallised twice from aqueous alcohol, giving needles, m. p. 68° (3 g.). Recrystallisation from light petroleum gave a *benziminazole* with m. p. 71° (Found: N, 7·5. $C_{22}H_{35}N_2Cl$ requires N, 7·7%). The *hydrochloride*, m. p. 211°, was prepared by passing dry hydrogen chloride into a solution of the base in benzene (Found: N, 7·0. $C_{22}H_{36}N_2Cl_2$ requires N, 7·0%).

β-(5-Chlorobenziminazol-2-yl)propionic Acid.—4-Chloro-*o*-phenylenediamine (14 g.) was heated in toluene (70 c.c.) with succinic anhydride (20 g.) for 1 hour (Chatterjee, *J.*, 1929, 2965). The precipitate obtained on cooling was dissolved in concentrated hydrochloric acid. Sodium hydroxide solution was

added until the solution grew turbid. Cooling the solution caused the deposition of brown crystals. Crystallisation from water (charcoal) afforded *p*-(5-chlorobenziminazol-2-yl)propionic acid, plates, m. p. 190—191° (12 g.). The *hydrochloride*, m. p. 257°, was obtained by the action of hydrogen chloride on a suspension of the base in chloroform (Found: N, 11·0. $C_{10}H_{10}O_2N_2Cl_2$ requires N, 10·7%).

5-Chloro-2-hydroxymethylbenziminazole.—4-Chloro-*o*-phenylenediamine (5·3 g.) and glycollic acid (3·9 g.) were heated for 30 minutes in 4*N*-hydrochloric acid (40 c.c.) (Phillips, *J.*, 1928, 2393). Neutralisation of the solution with aqueous ammonia gave a brownish crystalline product which had m. p. 205° after crystallisation from aqueous alcohol (5 g.). The *hydrochloride*, m. p. 246°, was precipitated from an acetone solution of the base by the action of hydrogen chloride (Found: C, 43·1; H, 3·6; N, 12·4. $C_8H_8ON_2Cl_2$ requires C, 43·0; H, 3·6; N, 12·6%).

5-Nitrobenziminazole.—4-Nitro-*o*-phenylenediamine (7 g.) was heated in formic acid solution (60 c.c.) with fused sodium formate (2 g.) for 30 minutes. Dilution of the solution, followed by neutralisation with aqueous ammonia, gave a precipitate which on crystallisation from aqueous alcohol gave 5-nitrobenziminazole (5 g.), yellow, m. p. 204—205° (cf. Bamberger and Berle, *Annalen*, 1891, **273**, 340).

4-Nitrobenziminazole.—Benziminazole (10 g.) was dissolved in nitric acid (*d* 1·42) cooled below 40°. Dilution of the solution and neutralisation with aqueous ammonia, followed by crystallisation of the precipitate from aqueous alcohol, afforded 4-nitrobenziminazole (7 g.), m. p. 210—212°. A mixture with 5-nitrobenziminazole had m. p. 198°.

5-Aminobenziminazole. 5-Nitrobenziminazole (2 g.) was reduced with hydrogen in alcoholic solution in the presence of Raney nickel. Filtration and evaporation of the alcohol afforded 5-aminobenziminazole (1·5 g.), m. p. 160° after crystallisation from aqueous alcohol (cf. Woolley, *loc. cit.*).

5-Nitro-2-mercaptobenziminazole.—4-Nitro-*o*-phenylenediamine (10 g.) was heated with carbon disulphide (7 g.) in alcohol (100 c.c.) for 3 hours in the presence of sodium hydroxide. The carbon disulphide and alcohol were removed under reduced pressure and the residue was crystallised from aqueous alcohol (charcoal), giving 5-nitro-2-mercaptobenziminazole (6 g.), m. p. 282° (Found: *N*, 21·2. Calc. for $C_7H_5O_2N_3S$: N, 21·5%).

5-Amino-2-mercaptobenziminazole.—5-Nitro-2-mercaptobenziminazole was reduced with hydrogen in alcoholic solution over Raney nickel. The nickel was removed by filtration and hydrogen chloride was passed into the alcoholic solution. Precipitation with ether, followed by crystallisation from water, afforded *5-amino-2-mercaptobenziminazole hydrochloride*, m. p. 220° (Found: C, 41·4; H, 4·0; S, 15·8. $C_7H_7N_3ClS$ requires C, 41·5; H, 4·4; S, 15·9%).

N-*p-Chlorophenyl-N'-(4-chloro-2-nitrophenyl)urea.*—4-Chloro-2-nitrophenyl *iso*cyanate (5 g.) was heated in toluene with *p*-chloroaniline (7 g.) and three drops of pyridine on the water-bath for 2 hours. On cooling of the solution a yellow precipitate formed, which on crystallisation from alcohol afforded N-*p-chlorophenyl-N'-(4-chloro-2-nitrophenyl)urea* (6 g.), yellow, m. p. 228° (Found: N, 12·9; Cl, 21·5. $C_{13}H_9O_3N_3Cl_2$ requires N, 12·9; Cl, 21·8%).

N-*p-Chlorophenyl-N'-(4-chloro-2-aminophenyl)urea.*—The above compound was reduced in ethyl acetate over Raney nickel with hydrogen under pressure. Removal of the nickel by filtration, followed by crystallisation of the product from alcohol gave N-*p-chlorophenyl-N'-(4-chloro-2-aminophenyl)urea*, m. p. 235° (Found: N, 14·0. $C_{13}H_{11}ON_3Cl_2$ requires N, 14·2%).

N-(*4-Chloro-2-nitrophenyl*)-N'-*isopropylurea.*—The reaction between 4-chloro-2-nitrophenyl *iso*cyanate and *iso*propylamine was carried out as described for *p*-chloroaniline. The *product* was yellow and had m. p. 183—184° (Found: N, 16·5. $C_{11}H_{13}O_3N_3Cl$ requires N, 16·3%).

N-*Pentamethylene-N'-(4-chloro-2-nitrophenyl)urea.*—The reaction between 4-chloro-2-nitrophenyl isocyanate and piperidine afforded a *product*, m. p. 89° (Found: N, 14·1. $C_{12}H_{14}O_3N_3Cl$ requires N, 14·8%).

Attempted Cyclisation of N-p-Chlorophenyl-N'-(4-chloro-2-aminophenyl)urea.—(*a*) The amine (6 g.) was heated in propionic acid (50 g.) with fused sodium acetate (2 g.) for 1 hour. The solution was diluted, made alkaline with 10% sodium hydroxide solution, and extracted with benzene. The benzene was removed *in vacuo* and the brownish residue crystallised from aqueous alcohol (charcoal) and then from carbon tetrachloride. The substance isolated in this way melted at 230°.

(*b*) The amine (5 g.) was heated in dry toluene (120 c.c.) with phosphorus oxychloride for 2 hours. After evaporation under reduced pressure the residue was crystallised twice from chloroform. The product obtained melted at 232°. A mixture of the product and *N'-p*-chlorophenyl-*N'*-(3-amino-4-chlorophenyl)urea melted at 235°.

(*c*) A solution of the base (3 g.) in dry toluene (100 c.c.) was heated with zinc chloride for 1 hour. The solution was cooled and filtered, and the toluene evaporated off. Repeated crystallisation of the residue from alcohol afforded a product melting at 230°. A mixture of the product and the original amine melted at 233°.

2-Hydroxybenziminazole.—A mixture of *o*-phenylenediamine (1 mol.) and urea (3 mols.) was heated at 170—180° (Kym and Ratner, *loc. cit.*) until the liquid had set to a hard crystalline mass. This was cooled, dissolved in 5% sodium hydroxide solution (charcoal), and precipitated with 30% hydrochloric acid, affording 2-hydroxybenziminazole as a micro-crystalline solid, m. p. 290° (70%).

5-Nitro-2-hydroxybenziminazole. 2-Hydroxybenziminazole (20 g.) was dissolved in nitric acid (*d* 1·42; 150 c.c.) at room temperature. After some minutes the solution became turbid and a yellow solid separated. The solution was poured on crushed ice and filtered and the solid crystallised from alcohol, affording the pale yellow 5-nitro-2-hydroxybenziminazole, m. p. > 295° in 75% yield (cf. Hagar, *Ber.*, 1884, **17**, 2630) (Found: N, 24·5. Calc. for $C_7H_5O_3N_3$: N, 23·5%).

The preparation was also carried out by fusing a mixture of 4-nitro-*o*-phenylenediamine and excess of urea at 170—180°. The cooled solid mass was dissolved in 5% sodium hydroxide solution (charcoal) to give a red solution; the colour disappeared on acidification and pale yellow 5-nitro-2-hydroxybenziminazole, m. p. > 290°, was precipitated (cf. Kym and Ratner, *loc. cit.*).

2-Chloro-5-nitrobenziminazole.—5-Nitro-2-hydroxybenziminazole (15 g.) was heated under reflux with phosphorus oxychloride (30 g.) until dissolution was complete (3 hours). After evaporation *in vacuo* the residual hardened foam was washed rapidly with ice-water and then crystallised from alkaline

aqueous alcohol. Cooling the solution caused the deposition of colourless 2-chloro-5-nitrobenziminazole, m. p. 220° (Kym and Ratner, *loc. cit.*).

5-Nitro-2-p-chloroanilinobenziminazole.—2-Chloro-5-nitrobenziminazole (10 g.) was heated at 180° with excess of *p*-chloroaniline (75 g.) for 2 hours. The dark brown melt was cooled and steam-distilled to remove the excess of *p*-chloroaniline, and the residue dissolved in concentrated hydrochloric acid. Neutralisation with aqueous ammonia afforded a yellowish-brown product (15 g.), which on crystallisation from alcohol gave *5-nitro-2-p-chloroanilinobenziminazole* as an orange-red micro-crystalline powder, m. p. 260° (decomp.) (Found: N, 19·8. $C_{13}H_9O_2N_4Cl$ requires N, 19·5%).

5-Nitro-2-piperidinobenziminazole.—2-Chloro-5-nitrobenziminazole (6 g.) was heated in piperidine (20 c.c.) for 2 hours. The residue obtained after evaporation of the piperidine was dissolved in concentrated hydrochloric acid and carefully neutralised with sodium carbonate. The orange-yellow precipitate obtained, crystallised from aqueous methanol, gave *5-nitro-2-piperidinobenziminazole* as small yellow needles, m. p. >260° (Found: N, 21·8. $C_{12}H_{14}O_2N_4$ requires N, 22·8%).

5-Amino-2-piperidinobenziminazole.—5-Nitro-2-piperidinobenziminazole (5 g.) was reduced in alcoholic solution with hydrogen in the presence of Raney nickel. Removal of the nickel and passage of hydrogen chloride, followed by addition of ether, precipitated the dihydrochloride. Crystallisation from water afforded *5-amino-2-piperidinobenziminazole dihydrochloride* as a trihydrate, m. p. 190° (Found: C, 42·8; H, 5·9; N, 16·4. $C_{12}H_{16}N_4Cl_2,3H_2O$ requires C, 42·2; H, 6·4; N, 16·4%).

1-(2-Pyridylaminomethyl)benziminazole.—Benziminazole (0·01 mol.) was dissolved in methyl alcohol (100 c.c.), together with 2-aminopyridine (0·011 mol.). 40% Aqueous formaldehyde (0·012 mol.) was added and the solution kept overnight (Bachman and Heisey, *J. Amer. Chem. Soc.*, 1946, **68**, 2406). Removal of the methyl alcohol by distillation, followed by crystallisation from aqueous alcohol, afforded *1-(2-pyridylaminomethyl)benziminazole* as needles, m. p. 190—192° (Found: C, 70·0; H, 5·5; N, 24·6. $C_{13}H_{12}N_4$ requires C, 69·7; H, 5·6; N, 24·9%).

4-Nitro-1-(2-pyridylaminomethyl)benziminazole.—Starting with 4-nitrobenziminazole the preparation was carried out as described above for benziminazole. Crystallisation of the product from aqueous alcohol afforded *4-nitro-1-(2-pyridylaminomethyl)benziminazole* as plates, m. p. 207—208° (Found: C, 58·0; H, 3·8. $C_{13}H_{11}O_2N_5$ requires C, 59·0; H, 4·1%).

4-Nitro-1-(2-hydroxyethylaminomethyl)benziminazole.—Under the conditions described above, ethanolamine, 4-nitrobenziminazole, and formaldehyde afforded 4-nitro-1-(2-hydroxyethylaminomethyl)-benziminazole as needles, m. p. 205°. The *monohydrochloride* had m. p. 260° (decomp.) (Found: N, 19·9. $C_{10}H_{13}O_3N_4Cl$ requires N, 20·6%).

5 : 6-Dinitro-2-hydroxybenziminazole.—5-Nitrobenziminazole (7 g.) was dissolved in fuming nitric acid (50 c.c.) (Kym and Ratner, *loc. cit.*). After 2 hours the solution was poured on crushed ice, and the yellow product dissolved in ammonia solution (*d* 0·88). After acidification with concentrated hydrochloric acid, followed by filtration, the solution deposited orange crystals of *5 : 6-dinitro-2-hydroxybenziminazole* (3 g.), which after crystallisation from alcohol did not melt up to 260° (Found: C, 37·6; H, 1·9; N, 24·0. Calc. for $C_7H_4O_5N_4$: C, 37·6; H, 1·8; N, 25·0%).

5 : 6 : 7-Trinitro-2-hydroxybenziminazole.—5-Nitro-2-hydroxybenziminazole (5 g.) was dissolved in concentrated sulphuric acid (50 c.c.), and concentrated nitric acid (*d* 1·42; 10 c.c.) added. After ½ hour, the solution was poured on crushed ice. The yellow precipitate (6 g.) was washed free from acid and dissolved in 10% sodium hydroxide solution, and the solution filtered and acidified. The resulting yellow solid dissolved in 5% sodium carbonate solution to give a deep-red solution. Cautious acidification with dilute hydrochloric acid afforded a crystalline orange-yellow precipitate of *5 : 6 : 7-trinitro-2-hydroxybenziminazole*, m. p. >300° (Found: C, 31·2; H, 1·2; N, 25·4. $C_7H_3O_7N_5$ requires C, 31·2; H, 1·1; N, 25·9%).

Reaction between p-Chloroanilino and 5 : 6-Dinitro-2-hydroxybenziminazole.—*p*-Chloroaniline (20 g.) was mixed with *5 : 6-dinitro-2-hydroxybenziminazole* (3 g.) and heated in a bath at 140° for 1 hour. The melt was cooled and then steam-distilled to remove excess of *p*-chloroaniline. The dark residue was dissolved in 3N-sodium hydroxide solution, and the solution filtered and acidified. The dark red product crystallised from aqueous alcohol to give a semi-crystalline mass which could be further fractionated by careful precipitation by acid of a solution in sodium carbonate solution. The products were all dark and contained from 38·0 to 52·0% of carbon and 22·0 to 25·0% of nitrogen. No substance corresponding to the expected nitro-*p*-chloroanilinobenziminazolone could be isolated. Slight antimalarial activity was displayed by the fractions.

Dinitro-p-chloroanilinobenziminazolone.—*5 : 6 : 7-Trinitrobenziminazolone* (5 g.) was heated with *p*-chloroaniline (30 g.) at 180° for 1 hour. Extraction of the solid product with dilute hydrochloric acid to remove excess of base, followed by dissolution of the residue in 10% sodium hydroxide solution, gave a reddish-purple solution. On acidification a red powder was precipitated; this was dissolved in dilute aqueous ammonia, and the solution filtered and acidified with dilute acid; a micro-crystalline precipitate of *dinitro-p-chloroanilinobenziminazolone*, m. p. >290° (Found: C, 44·2; H, 1·6; N, 19·8. $C_{13}H_6O_5N_5Cl$ requires C, 44·7; H, 2·3; N, 20·0%), was obtained.

Dinitroisopropylaminobenziminazolone.—Addition of *5 : 6 : 7-trinitrobenziminazolone* (5 g.) to *iso*propylamine (20 g.) provoked a violent reaction, giving a deep-red solution. When the reaction had ceased, the solution was diluted with alcohol and then acidified with dilute hydrochloric acid; there resulted an immediate precipitate of the bright red *dinitroisopropylaminobenziminazolone* (3 g.), m. p. 242° (Found: N, 25·1. $C_{10}H_{11}O_5N_5$ requires N, 25·0%).

6-Chloro-5-nitrobenziminazolone.—5-Chlorobenziminazolone (from 4-chloro-*o*-phenylenediamine and urea) was dissolved in nitric acid (*d* 1·42) at room temperature and set aside for 1 hour. The yellow precipitate obtained by pouring the acid solution on crushed ice was dissolved in 10% sodium carbonate solution, and the solution filtered. On acidification, *5-chloro-6-nitrobenziminazolone* was precipitated; it sinters at 200° (Found: N, 19·8. $C_7H_4O_3N_3Cl$ requires N, 19·6%).

2-Hydroxyglyoxalino(4' : 5'-5 : 6)benziminazole.—*5 : 6-Dinitrobenziminazolone* (6 g.) was reduced with iron filings and hydrochloric acid as described by Kym and Ratner (*loc. cit.*) to give *5 : 6-diaminobenziminazolone*. The dihydrochloride of the base was obtained as a brownish crystalline solid, and

without further purification was heated in formic acid solution with fused sodium formate. Neutralisation of the solution gave a dark precipitate which was dissolved in dilute hydrochloric acid. The solution was treated with charcoal, filtered, and evaporated almost to dryness *in vacuo*; this gave the hydrochloride of 2-hydroxyglyoxalino(4′ : 5′-5 : 6)benziminazole as needles, m. p. 280° (Found : N, 27·4. Calc. for $C_9H_8ON_2$,HCl : N, 26·6%).

(4 : 5-*Dihydroglyoxalin-2-ylthio*)*acetic acid.*—The reaction between 2-mercapto-4 : 5-dihydroglyoxaline and chloroacetic acid as described by Johnson and Edens (*J. Amer. Chem. Soc.*, 1942, **64**, 2706) afforded 4 : 5-dihydroglyoxaline-2-thiolacetic acid hydrochloride, m. p. 222° after crystallisation from alcohol (Found : C, 30·8; H, 4·9; N, 13·6. Calc. for $C_5H_8O_2N_2S$,HCl : C, 30·8; H, 4·6; N, 14·3%).

Bis-4 : 5-*dihydroglyoxalin-2-yl Disulphide Periodide.*—2-Mercapto-4 : 5-dihydroglyoxaline, treated with iodine in potassium iodide solution (Johnson and Edens, *loc. cit.*) gave the periodide, m. p. 118°.

Bis-4 : 5-*dihydroglyoxalin-2-yl Sulphide.*—The above periodide, digested with boiling water (Johnson and Edens, *loc. cit.*), gave bis-4 : 5-dihydroglyoxalin-2-yl sulphide as its hydriodide, m. p. 282° (Found : N, 18·7. Calc. for $C_6H_{10}N_4S$,HI : N, 18·8%).

2-*Mercapto*-1-*piperidinomethyl*-4 : 5-*dihydroglyoxaline.*—2-Mercapto-4 : 5-dihydroglyoxaline was treated with formaldehyde and piperidine in methyl alcohol as described before. The base had m. p. 118°. The *dihydrochloride*, m. p. 200°, was prepared by the action of hydrogen chloride on an alcoholic solution of the base (Found : N, 15·0. $C_9H_{15}N_3SCl_2$ requires N, 15·4%).

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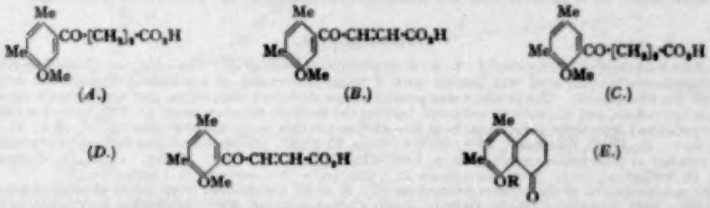
315. *The Constitution of ψ-Santonin. A Correction to Part III.*

By WESLEY COCKER, CYRIL LIPMAN, and D. R. A. WHYTE.

The products of condensation of *m*-4-xylyl methyl ether with succinic and maleic anhydrides are respectively β-(5-methoxy-2 : 4-dimethylbenzoyl)-propionic acid (*A*) and -acrylic acid (*B*), and not β-(2-methoxy-3 : 5-dimethylbenzoyl)-propionic (*C*) and -acrylic acids (*D*) as stated by Cocker and Lipman (*J.*, 1947, 533).

IN an earlier communication, Cocker and Lipman (*loc. cit.*) assumed that succinic and maleic anhydrides condense with *m*-4-xylyl methyl ether in the *ortho*-position to the methoxy-group. It has now been shown by oxidation of the products to 5-methoxy-2 : 4-dimethylbenzoic acid (cf. Cocker *et al.*, in the press) that condensation takes place predominantly at the *meta*-position to the methoxy-group, thus confirming the work of von Auwers and Mauss (*Ber.*, 1928, **61**, 1495) (previously overlooked by Cocker and Lipman) who showed that reaction of acyl chlorides with *m*-4-xylyl methyl ether gave mainly 5-methoxy-2 : 4-dimethylphenyl ketones. This development involves the re-orientation of a number of compounds, described by Cocker and Lipman, which were derived from the initial condensation products, β-(5-methoxy-2 : 4-dimethylbenzoyl)-propionic (*A*) and -acrylic acids (*B*) respectively.



Reduction of (*A*) affords γ-(5-methoxy-2 : 4-dimethyl)phenylbutyric acid * which on cyclisation with concentrated sulphuric acid at 65° yields almost pure 1-keto-8-methoxy-5 : 7-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (*E*; R = Me), whilst 80% sulphuric acid on the water-bath affords a mixture in which the hydroxy-compound (*E*; R = H) predominates. The subsequent stages in the production of 2 : 4-dimethyl-1-naphthol (Cornforth, Cornforth, and Robinson, *J.*, 1943, 168; Clemo and Cocker, *J.*, 1946, 30; Cocker and Lipman, *loc. cit.*) are unaffected by the new orientation.

* This acid, stated to have m. p. 92°, has been obtained in another modification, m. p. 120°. Both, however, yield the same hydroxy-butyric acid, m. p. 116—117°, on demethylation (Cocker and Lipman, *loc. cit.*).

Cocker and Lipman (*loc. cit.*) described the tetralone, m. p. 61·5°, obtained by the use of 80% sulphuric acid as 1-keto-5-methoxy-6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene. Later work has shown that the tetralone was in fact a hydroxy-compound now known to be (*E*; R = H). Its methyl ether (*E*; R = Me) melts at 41—42°. There seems to have been some confusion at this point in the earlier work since the semicarbazone, glyoxylate, and bromotetralone described were correctly formulated as methoxy-compounds. The piperonylidene derivative was undoubtedly a hydroxy-compound and the analytical figures given in the earlier paper are in good agreement with this view. We have been unable to obtain the hydroxytetralone, m. p. 145°, previously described.

Cocker and Lipman's tetralone gave a violet ferric chloride colour, but was insoluble in sodium hydroxide solution, and a methoxyl determination performed by other workers gave a value in good agreement with that expected for the methoxy-tetralone. At the time, it was concluded that enolisation was responsible for the ferric chloride reaction, whereas we now know that the colour was associated with the phenolic group. The insolubility of the tetralone in aqueous sodium hydroxide is a result of steric hindrance; thus, for example, 2 : 4-dimethyl-6-*tert.*-butylphenol is sparingly soluble in all but the strongest alkali. The liquid tetralone used in the preparation of derivatives was actually a mixture of hydroxy- and methoxy-compounds and not a mixture of keto and enol forms.

We have now prepared the semicarbazone of the hydroxy-tetralone (*E*; R = H) and the piperonylidene derivative of its methyl ether (*E*; R = Me). 5-Hydroxy-6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene was obtained from both the tetralones (*E*; R = H or Me) and was readily dehydrogenated to 2 : 4-dimethyl-1-naphthol.

In addition to the compounds mentioned above, the various products described by Cocker and Lipman (*loc. cit.*), who denoted them by the numbers in parenthesis, have to be re-orientated as follows:

Route A.—2-Bromo-1-keto-8-methoxy-5 : 7-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (VIII).

Route B.—Ethyl 1-keto-8-methoxy-5 : 7-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-glyoxylate (XI) and -carboxylate (XII).

Route C.—Ethyl α-chloro-β-(5-methoxy-2 : 4-dimethylbenzoyl)propionate (XIV). Ethyl α-(5-methoxy-2 : 4-dimethylbenzoyl)butane-βγγ-tricarboxylate (XV). α-(5-Methoxy-2 : 4-dimethylbenzoyl)butane-βγ-dicarboxylic acid (XVI). α-(β-5-Methoxy-2 : 4-dimethylphenylethyl)-α′-methylsuccinic acid (XVII). Lactone of 1-keto-8-methoxy-5 : 7-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-α-propionic acid (III; R = Me).

Re-orientation of the methoxy-dimethylacetophenone, m. p. 76°, described by Cocker and Lipman (*loc. cit.*), leads to 5-methoxy-2 : 4-dimethylacetophenone. The melting point of this ketone is given by von Auwers and Mauss (*loc. cit.*) as 50—51°, and a specimen recently prepared in these laboratories had m. p. 52°; consequently the constitution of this ketone, m. p. 76°, is still uncertain. It is possible that the difference in melting point is due to dimorphism.

Experimental.

1-*Keto-8-methoxy-5 : 7-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene* (*E*; R = Me).—γ-(5-Methoxy-2 : 4-dimethylphenyl)butyric acid was heated with 5 times its weight of concentrated sulphuric acid at 65—70° for 10 minutes. The product was poured on ice, collected with ether, and washed with aqueous sodium hydroxide, and the solvent removed, leaving the *methoxy-tetralone* as an oil (20%) which solidified and crystallised from light petroleum (b. p. 40—60°) as needles, m. p. 41—42° (Found: C, 76·5; H, 7·8; OMe, 14·7. $C_{15}H_{18}O_2$ requires C, 76·5; H, 7·8; OMe, 15·2%). Its *piperonylidene* derivative crystallised from alcohol as pale yellow needles, m. p. 112—113° (Found: C, 75·1; H, 5·8. $C_{31}H_{30}O_4$ requires C, 75·0; H, 5·9%).

The *semicarbazone* of the hydroxy-tetralone (*E*; R = H) crystallised from dilute alcohol as needles, m. p. 273—275° (Found: C, 65·5; H, 6·9. $C_{13}H_{17}O_2N_3$ requires C, 63·2; H, 6·9%).

5-Hydroxy-6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene.—Obtained by the demethylation of its methyl ether, this *hydroxy*-compound crystallised from light petroleum (b. p. 40—60°) as needles, m. p. 76—76·5° (Found: C, 82·25; H, 8·9. $C_{12}H_{16}O$ requires C, 81·8; H, 9·1%).

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316. *Adsorption of Organic Bases on Silica Gel, and Heats of Adsorption. Part II.*

By B. P. Gyani.

The adsorption of diethylamine, triethylamine, pyridine, α-picoline and piperidine on silica gel has been measured at 35°. The heats of adsorption have been determined by a tensimetric method. The entropy changes accompanying desorption are similar to those accompanying evaporation of the free liquid.

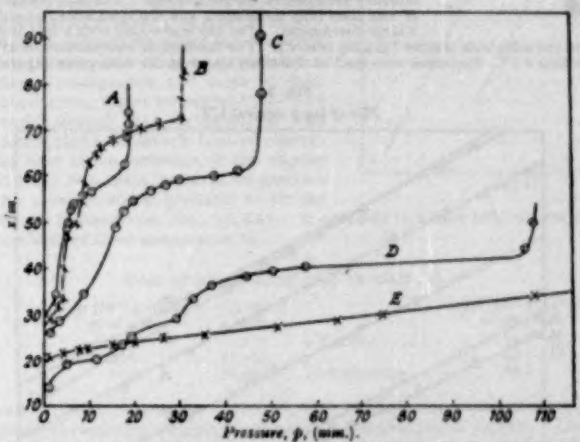
In a previous paper (*J. Indian Chem. Soc.*, 1949, **26**, 345) measurements of the heat of adsorption of methyl alcohol and its homologues on silica gel have been described. The primary object of the present investigations was to see whether any marked changes in the adsorption isotherms and heats of adsorption are produced when bases are substituted for the alcohols.

Experimental.

The silica gel was prepared by mixing, with vigorous shaking, equal volumes of commercial hydrochloric acid, diluted to *d* 1·05, and commercial sodium silicate syrup diluted with water to *d* 1·12. The resulting sol was allowed to set at about 30°, then cut into small pieces, washed thoroughly, and dehydrated gradually at increasing temperatures. The final desiccation was at 350° in a current of dry air. The gel was about two years old at the time of the measurements. The liquids were purified according to standard methods before use and had satisfactory b. p.s. The gel was evacuated at about 300°, cooled, and flushed several times with the appropriate vapour before the observations were recorded. An oil-pump giving a vacuum of 0·001 mm. was used for evacuating the gel and no attempt was made to improve the vacuum.

Fig. 1.

Adsorption isotherms.



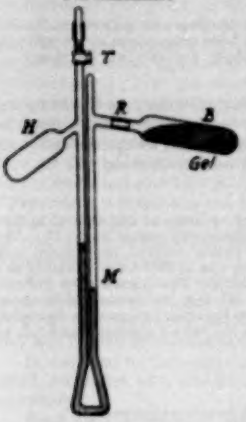
A, α-Picoline; B, pyridine; C, piperidine; D, triethylamine; E, diethylamine.

The adsorption was measured in an apparatus previously described (*J. Physical Chem.*, 1945, **49**, 226). The amounts of adsorption at different pressures of the vapour were measured by noting the increase in the weight of a fixed amount of the gel (about 4 g.) contained in a detachable bulb weighing about 15 g. At half saturation of the gel the amount of adsorption was well over 1 g. in each case. The bulb had a fixed dead space of less than 2 c.c. A vapour having a molecular weight of 100 occupying this dead space at a pressure of 100 mm. would weigh less than 0·001 g. at the temperature of these experiments, so that the error in determining the amount of adsorption was in general less than 0·1%. The pressure of the vapour was measured on a simple mercury manometer. By a short-range telescope pressures were read on a metre scale directly attached to the manometer, with an accuracy of ±0·1 mm. The adsorption bulb was enclosed in an air thermostat whose temperature was kept constant at 35° ± 0·1°.

Fig. 1 shows the plot of the amount of adsorption per g. of the gel, x/m, against pressure p of the vapour. x has been expressed in 10^{-4} g.-mol. of the liquid and p in mm. of mercury. The data plotted refer to desorption only. These isotherms were found to be satisfactorily reproducible. The

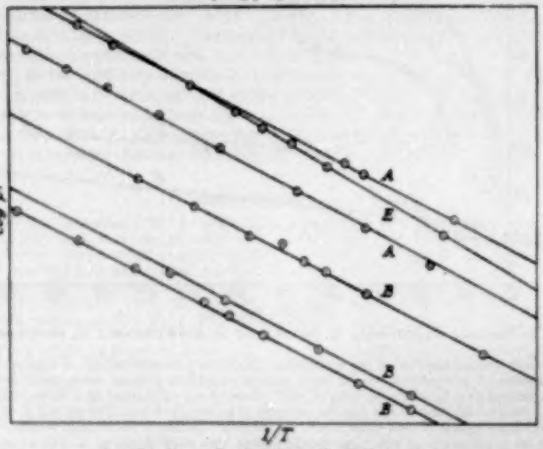
adsorption isotherms were a little erratic in the beginning but gradually settled down in the neighbourhood of the desorption isotherms except for small regions of hysteresis towards saturation pressures. It is surprising that the isotherms for the different bases are not similar in shape. The simplest isotherm is given by diethylamine which appears to belong to type I described by Brunauer ("The Adsorption of Gases and Vapour," Vol. I, Oxford Univ. Press, 1943, p. 150). The piperidine and α-picoline curves are sigmoid, corresponding to type IV. The remaining two isotherms have a number of distinct loops and correspond to none of the types described by Brunauer. Somewhat similar discontinuities in the adsorption isotherms of alcohols on silica gel have been observed by the author earlier (*J. Physical Chem.*, 1945, **49**, 226).

FIG. 2.
The tensimeter.



Isosteric Heats of Adsorption.—The heats of adsorption on the same sample of the gel were obtained by a tensimeter. The apparatus is shown in Fig. 2. The adsorption bulb containing the gel was sealed to one limb of the manometer *M*. A glass rod placed between two slight constrictions at *R* prevented the gel particles from falling into the manometer during handling. Another small bulb *H* was sealed to the other limb of the manometer. Sufficient mercury was introduced into the apparatus to fill half the manometer on either side. It was then collected into *H* by tilting the apparatus. *B* was then heated to about 300° while the apparatus was being evacuated with an oil-pump. When the evacuation was complete the tap *T* was closed and the bulb allowed to cool. A quantity of the freshly distilled liquid under investigation was introduced into the apparatus. The vapour was rapidly absorbed by the gel, and the process was aided by cooling. The excess of liquid which collected in *B* was heated almost to boiling and kept at that temperature for some minutes to get rid of the gases retained by the gel during heating and evacuation. The excess of liquid was then pumped out, the tap *T* closed, and the mercury returned to the manometer. The manometer on the side of *H* was then fully evacuated, and the apparatus clamped vertically in a large thermostat. The tap was sealed with a few drops of mercury and painted on the sides with molten Faraday cement. The thermostat was maintained at temperatures constant to within 0·1°. Pressures were read as described above in the adsorption experiments.

FIG. 3.
Plot of log p *against* 1/T.



A, α-Picoline ; B, pyridine ; E, diethylamine.

The thermostat was set at different temperatures (room temperature to about 70°) and the pressures of the vapour in contact with the gel at these temperatures were read to the nearest 0·1 mm. After completion of runs at an arbitrarily fixed composition the tensimeter was removed from the thermostat. The mercury was again collected in *H* and a quantity of the vapour was pumped out from the gel to reduce the amount of adsorption. The apparatus was then reset for another run. The value of the adsorption, *x*/*m*, was computed by reference to the previously determined isotherms at 35°.

Reproducibility in these experiments was good. Different runs at a fixed amount of adsorption rarely showed a pressure difference of 1 mm. at the same temperature. The measurements were performed with different quantities of the gel in the bulb and some of the measurements were checked by a duplicate apparatus. One can therefore be sure that the results were not vitiated owing to presence of the dead space inside the apparatus (which at any rate was small) or by non-uniformity of the gel.

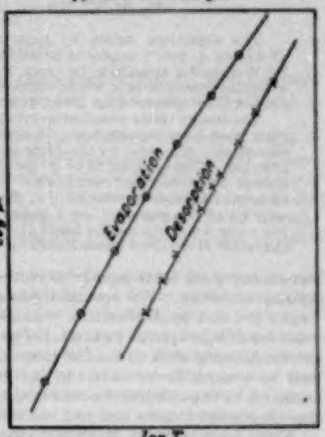
Results.

The isosteric heat of adsorption, Q, was calculated from the equation, $\mathrm{d}\log p/\mathrm{d}(1/T) = -Q/2{\cdot}303R$, which shows that the plot of $\log p$ against $1/T$ should be a straight line if Q is constant under the conditions of the experiments. Fig. 3 shows some of these plots for the various bases and the lines are satisfactorily straight. This means that the isosteric heat has no observable temperature coefficient. Brunauer (*op. cit.*, p. 262) calls attention to the fact that, if adsorption may be regarded as purely physical, the heat of adsorption should be practically temperature-independent.

The average values of $-Q$ for the bases pyridine, α-picoline, and diethylamine at different stages of adsorption are summarised in the Table. They are practically equal for all three compounds. It was not possible to measure $-Q$ for diethylamine at higher values of x/m owing to its larger equilibrium pressures. It is also seen that the heat values are not markedly different from those for the alcohols (methyl alcohol, 11470 at $x/m = 23{\cdot}97$; ethyl alcohol about 11500 for x/m varying from 87 to 40). The comparison is interesting when one considers the differences between the chemical properties of the two series of compounds and some of their physical properties, *e.g.*, dipole moments, 1·73—1·65 for methyl–butyl alcohol, 2·11 for pyridine. The net heat of adsorption (= isosteric heat of adsorption − latent heat of condensation of the vapour to a liquid in bulk) was again found to be positive throughout for pyridine and is probably so for the other bases (cf. *J. Indian Chem. Soc., loc. cit.*). It amounts to about 18% of the isosteric heat under the conditions of these measurements.

Fig. 4.

Entropies of evaporation and desorption of pyridine on silica gel.



Heats of adsorption of bases on silica gel.

	x/m (10^{-4} g.-mol./g. of gel).	$-Q$, cals./g.-mol.		x/m (10^{-4} g.-mol./g. of gel).	$-Q$, cals./g.-mol.
Pyridine	71·5	11,270	α-Picoline	54·9	11,920
	68·0	11,850		53·1	11,020
	64·0	11,660	Diethylamine ...	22·1	12,010

Hildebrand (*J. Amer. Chem. Soc.*, 1915, **37**, 970) employs the equation $\mathrm{d}\log p/\mathrm{d}\log T = A/RT$ to discuss the entropy changes accompanying evaporation of liquids. The quantity A has been called the entropy of evaporation; p is the vapour pressure of the liquid at the absolute temperature T. The quantity A/R which is proportional to the entropy may be obtained at any temperature T by plotting $\log p$ against $\log T$, and measuring the slope of the resulting curve at the appropriate point. A similar procedure may be adopted with the data obtained in the present tensimetric measurements to see how far the entropy changes accompanying evaporation are analogous to those accompanying desorption. The upper curve of Fig. 4 refers to evaporation of liquid pyridine in bulk, the vapour-pressure data being those of Mann (*J. Amer. Chem. Soc.*, 1931, **53**, 453); the lower curve refers to the desorption of the same liquid from silica gel at constant amount of adsorption, 64 × 10^{-4} g.-mols. per g. of the gel. One notes that the entropy of evaporation falls off somewhat towards higher temperatures but that the entropy of desorption of the same liquid from silica gel, at a constant amount of adsorption is steady in the range of temperatures covered. However, the two curves have substantially equal slopes. This result may be interpreted to mean that the adsorbed molecules

behave in a manner similar to, but not identical with, that in the ordinary liquid state with regard to the degrees of freedom.

The author is grateful to the Patna University for the award of a Research Fellowship which made this work possible. He is also deeply indebted to his colleague Professor G. P. Dube for valuable discussions.

SCIENCE COLLEGE, PATNA 5, INDIA. [*Received, September 16th*, 1949.]

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317. *The Dissociation Energy of Fluorine.*•

By M. G. EVANS, E. WARHURST, and E. WHITTLE.

The objections raised by some authors to von Wartenberg's evaluation of $D(F_2) = 63{\cdot}5$ kcals. g.-mol.$^{-1}$ appear to be well founded. Recent work by Schmitz and Schumacher and by Wahrhaftig appears to be much more reliable. It is concluded that the experimental data *at present available* as a whole indicate strongly a value for $D(F_2)$ of about 37 kcals. g.-mol.$^{-1}$, certainly not greater than about 45 kcals. g.-mol.$^{-1}$.

The energy terms which enter into the calculation of electron affinities using the Born–Haber cycle have been re-examined. It is considered that a value of $D(F_2) = 37$ kcals. g.-mol.$^{-1}$ leads inescapably to a value for the electron affinity of *gaseous* fluorine atoms which is less than that of chlorine. There appear to be no uncertainties in the various energy terms which could be large enough to reverse this conclusion. On the other hand, it has been shown that the electron affinity of fluorine in solution (*i.e.*, the electron affinity of the gaseous atom plus the heat of solution of the negative ion) remains larger than that of chlorine. The effects of changes in the value for $D(F_2)$ on the heats of a number of simple processes of interest and on the ionic character of covalent bonds involving fluorine have been discussed.

PUBLISHED work leads mainly to two widely different values for the dissociation energy of the fluorine molecule. The spectroscopic studies on fluorine by von Wartenberg, Sprenger, and Taylor (1), and by Bodenstein, Jockusch, and Sing Hou Chong (2) are considered to indicate a value for $D(F_2)$ of about 64 kcals. per g.-mol. On the other hand, more recent spectroscopic and thermochemical work on the ClF molecule by Wahrhaftig (3) and by Schmitz and Schumacher (4) lead to a much lower value, in the neighbourhood of 33 kcals. Very recently Barrow and Caunt (5) have published the results of spectroscopic work with RbF and CsF and have concluded that their observations lead to a value for $D(F_2)$ of about 50 kcals.

There have been few published attempts to assess the reliability of the different claims and it seemed to us that such a survey would be useful, particularly since a number of other important energy quantities, such as the electron affinity of the fluorine atom and certain bond energies, are dependent on the value of $D(F_2)$.

The Spectrum of Fluorine.—The estimate of $D(F_2) = 63{\cdot}3$ kcals. by von Wartenberg, Sprenger, and Taylor (1) was based on the following considerations. The absorption spectrum of fluorine is entirely continuous, whereas the spectra of the remaining halogens show both a continuum and a band system. Thus $D(F_2)$ cannot be estimated by a band-convergence method. Von Wartenberg, Sprenger, and Taylor listed, for all four halogens, the values then available for λ_m, the wave-lengths at which the continuum shows a maximum absorption. In the cases of Cl_2, Br_2, and I_2 they also listed the available values for λ_c, the convergence limit of the band system. A plot of $\lambda_c - \lambda_m$ against atomic number gave a straight line. Extrapolation of this line gave a value of $\lambda_c - \lambda_m$ for fluorine from which λ_c and hence $D(F_2)$ were derived.

These authors pointed out that this method had no theoretical basis. Such a straight line requires the existence of extremely special relations between the potential energy curves of the ground and the excited states for the series of molecules, Cl_2, Br_2, and I_2. It is difficult to see why such a connection should exist. Mulliken (6) has also criticised both the data and the theoretical basis of this method.

There are two other high values for $D(F_2)$ in the literature. The value of 70 kcals. deduced by Bodenstein *et al.* (2) is not an observation; it is based merely on an interpolation from a smooth curve of $D(X_2)$ against the atomic number of X for the series H_2, Cl_2, Br_2, and I_2. From a study of the long-wave-length continua of LiF, NaF, and KF, Desai (7) deduced a value of 72 kcals. for $D(F_2)$. Gaydon (8) has pointed out that this estimate is worthless since it is based on old thermochemical data now known to be incorrect. Using recent thermochemical data, Gaydon found that Desai's spectroscopic results lead to $D(F_2) = 24$, 48, and 62 kcals. from LiF, NaF,

• Based on a paper read at the Symposium on "Fluorine Chemistry" on November 30th, 1949.

and KF, respectively. Very little can be concluded from such scattered results, except perhaps that $D(F_2)$ is not as high as von Wartenberg's value.

The Thermochemistry and Spectrum of ClF.—The first observations in serious conflict with $D(F_2) = 63{\cdot}3$ kcals. were provided by Wahrhaftig's work (3) on the absorption spectrum of ClF. He observed 13 bands with a good convergence limit and found that $D(ClF) = 60{\cdot}3$ kcals., on the assumption that dissociation to excited fluorine atoms occurs. If $Q_f(ClF)_g$ is the heat of formation of gaseous ClF from the elements in their standard states,* we have

$$Q_f(ClF)_g - D(ClF) + \tfrac{1}{2}D(Cl_2) + \tfrac{1}{2}D(F_2) = 0 \quad \ldots\ldots\ldots \quad (1)$$

The values of the dissociation energies refer to absolute zero whereas the heats of formation refer to room temperature. However, the correction is negligible compared to the uncertainties in some of the data used.

If $D(Cl_2) = 57{\cdot}1$ kcals. (8) and $D(ClF) = 60{\cdot}3$ kcals. (3),

then $$D(F_2) = 63{\cdot}4 - 2Q_f(ClF)_g \text{ kcals.}$$

At the time of the appearance of Wahrhaftig's paper, two values of $Q_f(ClF)_g$ were available from thermochemical experiments, *viz.*, 27·4 (9) and >22 kcals. (10) These values give $D(F_2) = 8{\cdot}6$ and $<19{\cdot}4$ kcals., respectively.

Gaydon (8) has drawn attention to another feature which he considers indicates a value of $D(F_2)$ less than 63·3 kcals. Data are available for the first five vibrational levels of the ground state of HF. (11) The usual Birge–Sponer plot shows a marked positive curvature and hence it would be expected that $D(HF)$ would lie *below* the value of 138 kcals. obtained by a linear extrapolation. Gaydon points out that the values of $D(F_2)$ and $D(HF)$ are linked thermochemically by the value of $Q_f(HF)_g$. $D(F_2) = 63{\cdot}3$ kcals. leads to $D(HF) = 147$ kcals., a value *higher* than the linear extrapolation value.

The spectroscopic and thermochemical work of Schmitz and Schumacher (4) provides the strongest evidence for a value of $D(F_2)$ much lower than 63·3 kcals. These authors repeated Wahrhaftig's work (3) on the absorption spectrum of ClF. The ClF was prepared in two ways: (*a*) directly from pure Cl_2 and F_2, and (*b*) by mixing ClF_3 and Cl_2 in the correct proportions in the absorption cell at 350°. The two samples gave the same spectrum. The absorption measurements were carried out at room temperature and 1·5 atmospheres pressure, thus ensuring that the transitions to the upper electronic state originated almost entirely from the zeroth vibrational level of the ground state. It seems very unlikely that there can be much error in the assessment of the convergence limit in this case since transitions were observed to 14 vibrational levels of the upper state, which possesses a very shallow hollow in the potential-energy curve.

Schmitz and Schumacher used three different extrapolation methods, which give a maximum divergence of 0·8 kcals. in the value for D'_e, the dissociation energy of this upper state (5·0—5·8 kcals.). Wahrhaftig (3) gives 5·0 kcals. for this quantity, but it is unlikely that the uncertainty in the convergence limit itself is as large as the difference between these estimates of D'_e. The value of D''_e, the dissociation energy of the ground state, is uncertain because it is not known which of the dissociation products is in an excited state. However, this uncertainty is not large since both atomic excitation energies are small (F 1·1, and Cl 2·5 kcals.).

Schmitz and Schumacher's work thus yields a range of values for D''_e, depending on the mode of extrapolation and the assumption concerning the atomic excitation. The values range from 58·4 to 60·7 kcals. Wahrhaftig's data yield the values 58·9 or 60·3 kcals. respectively, depending on whether an excited chlorine or fluorine atom is produced. Hence a value of $D(ClF) = 59{\cdot}6 \pm 1{\cdot}2$ kcals. can be open to very little uncertainty.

Schmitz and Schumacher also measured $Q_f(ClF)_g$, so that $D(F_2)$ could be evaluated from the equation given above. $Q_f(ClF)_g$ was obtained by measuring the heats of the following two reactions:

$$(NaCl)_c + \tfrac{1}{2}F_2 \longrightarrow (NaF)_c + \tfrac{1}{2}Cl_2 \qquad Q_1 = 39{\cdot}5 \pm 0{\cdot}5 \text{ kcals.}$$
$$(NaCl)_c + ClF \longrightarrow (NaF)_c + Cl_2 \qquad Q_2 = 24{\cdot}5 \pm 0{\cdot}1 \text{ kcals.}$$

The figure for Q_1 included a correction for a small quantity of ClF_3 which was formed. The Q_2 value was the mean of ten experiments. Von Wartenberg and Fitzner (12) had previously measured Q_1 and obtained $39{\cdot}3 \pm 0{\cdot}1$ kcals., a result in very close agreement with the above. Another, quite independent, estimate of Q_1 can be made from the Q_f values of $(NaCl)_g$ and $(NaF)_c$. It is clear that $Q_1 = Q_f(NaF)_c - Q_f(NaCl)_c$. The Q_f values given by Rossini and Bichowski (13) (which have each been obtained by indirect methods involving heats of solution

* Q will be used throughout to indicate heats of formation from the elements in their standard states.

and neutralisation, etc.) give $Q_1 = 37{\cdot}7$ kcals. These three estimates seem to establish $Q_1 = 38{\cdot}7 \pm 1{\cdot}0$ kcals. with a considerable degree of certainty.

A second evaluation of Q_2 may be made in the following way. Schmitz and Schumacher (4) have determined the heat of the reaction :

$$ClF + F_2 \longrightarrow ClF_3 \qquad Q_3 = 25 \pm 2 \text{ kcals.}$$

from the temperature dependence of the equilibrium constant. They also measured directly the heat of the reaction :

$$3(NaCl)_c + ClF_3 \longrightarrow 3(NaF)_c + 2Cl_2 \qquad Q_4 = 76{\cdot}5 \text{ kcals.} \quad \text{(No accuracy limits given)}$$

We have thus $Q_2 = Q_4 + Q_3 - 2Q_1 = 24{\cdot}1 \pm \sim 4$ kcals.

Wicke and Schäfer (14) have independently determined Q_2 from the temperature dependence of the equilibrium constant. Their value is $Q_2 = 26{\cdot}5 \pm 0{\cdot}5$ kcals. Combining this with Q_1 and Q_4 we obtain $Q_3 = 25{\cdot}6 \pm \sim 2{\cdot}5$ kcals. These latter estimates of Q_2 add considerable support to the figure obtained by the direct determination. However, they involve data from experiments which Schmitz and Schumacher state to be less accurate than the direct determinations of Q_1 and Q_4. Accordingly the evaluation of $Q_f(ClF)_g = Q_1 - Q_2$ has been carried out by using $Q_2 = 24{\cdot}5 \pm 0{\cdot}1$ kcals. and the above average value of $Q_1 = 38{\cdot}7 \pm 1{\cdot}0$ kcals. This gives $Q_f(ClF)_g = 14{\cdot}2 \pm 1{\cdot}1$ kcals. Wicke (15) has recently measured directly the heat of formation of ClF from the elements. By pressure measurements he has shown that, under the conditions of his experiments, no ClF_3 was formed. He obtained $Q_f(ClF)_g = 11{\cdot}6 \pm 0{\cdot}4$ kcals. Combining this with the above value to cover the whole range of uncertainty gives $Q_f(ClF)_g = 13{\cdot}3 \pm 2{\cdot}1$ kcals.

Introducing this value into equation (1), together with $D(ClF) = 59{\cdot}6 \pm 1{\cdot}2$ and $D(Cl_2) = 57{\cdot}1$ kcals., gives :

$$D(F_2) = 36{\cdot}4 \pm 7{\cdot}6 \text{ kcals.}$$

Table I summarises the data used in deriving this figure for $D(F_2)$.

TABLE I.

$$\begin{aligned}
(NaCl)_c + \tfrac{1}{2}F_2 &\longrightarrow (NaF)_c + \tfrac{1}{2}Cl_2 \quad Q_1\\
(NaCl)_c + ClF &\longrightarrow (NaF)_c + Cl_2 \quad Q_2\\
ClF + F_2 &\longrightarrow ClF_3 \quad Q_3\\
3(NaCl)_c + ClF_3 &\longrightarrow 3(NaF)_c + 2Cl_2 \quad Q_4
\end{aligned}$$

Q_1	Method.	Q_2	Method.
$39{\cdot}3 \pm 0{\cdot}1$	Direct, v. W. and F. (12)	$24{\cdot}5 \pm 0{\cdot}1$	Direct, S. and S. (4)
$39{\cdot}5 \pm 0{\cdot}5$	Direct, S. and S. (4)	$24{\cdot}1 \pm \sim 4$	From Q_3 (4) and Q_4 (4)
37·7	Indirect, R. and B. (13)	$25{\cdot}6 \pm \sim 2{\cdot}5$	From Q_3 (4) and Q_4 (14)
Q_1 chosen $= 38{\cdot}7 \pm 1{\cdot}0$ kcals.		Q_2 chosen $= 24{\cdot}5 \pm 0{\cdot}1$ kcals.	

$Q_f(ClF)_g = Q_1 - Q_2 = 14{\cdot}2 \pm 1{\cdot}1$ kcals.
$Q_f(ClF)_g = 11{\cdot}6 \pm 0{\cdot}4$ kcals., Wicke (15).
$Q_f(ClF)_g$ chosen $= 13{\cdot}3 \pm 2{\cdot}1$ kcals.
$D(ClF)$ chosen $= 59{\cdot}6 \pm 1{\cdot}2$ kcals.

$$D(F_2) = 36{\cdot}4 \pm 7{\cdot}6 \text{ kcals.}$$

This range of values includes all the uncertainties in the various quantities used. It does not include the older estimates of $Q_f(ClF)_g$, *viz.*, 27·4 (9) and >22 kcals. (10). Inclusion of these figures would give a result for $D(F_2)$ *lower* than the above value with a wider range of uncertainty.

We consider that the figure which we have chosen for the heat of formation of $(ClF)_g$ cannot be seriously in error. The number of independent observations involved is fairly considerable and forms a convincing body of data. Likewise the value chosen for $D(ClF)$ seems to be open to little uncertainty, unless the *interpretation* of the spectrum of this molecule is seriously in error. Wicke (16) has suggested that this is, indeed, the case. He give the following argument.

If Morse curves are constructed for the upper and lower states of the chlorine molecule, using the known constants, a fairly good estimate can be obtained for the frequency of the intensity maximum in the continuous spectrum. This is obtained, using the Franck–Condon principle, by finding the point at which a vertical line, drawn from the minimum of the lower-state potential-energy curve, cuts the repulsion side of the Morse curve for the upper state. The estimated $h\nu_{max.}$ is less than the observed value by less than 10 kcals., in terms of energy. Wicke points out that the same procedure applied to the case of ClF, using the constants given by Wahrhaftig (3), gives a calculated value for $h\nu_{max.}$ about 40 kcals. lower than the experimental

value reported by Schmitz and Schumacher (4). Wicke, therefore, concludes that considerable doubt attaches to the figure $D(ClF) \simeq 60$ kcals. which has been obtained from this spectrum.

Wicke's conclusion appears to us by no means sure. It is well known that a Morse curve is merely an approximation, even in the region below the dissociation limit. Above this limit the Morse curve will be an even more uncertain approximation, and this, we feel, will be particularly exaggerated for curves which possess very shallow minima. We do not consider, therefore, that a poor result for a particular example of this type of calculation, which is concerned with features of the continuous spectrum, impairs the conclusions drawn from the band convergence which lies in quite a different region of the spectrum. It is difficult to envisage a more plausible interpretation of these bands than the one which has been suggested by the original observers.

Recently Barrow and Caunt (5) have measured the heats of dissociation of gaseous RbF and CsF. $D(F_2)$ may be estimated from these observations, since

$$\tfrac{1}{2}D(F_2) = D(MF) + L(MF) - L(M) + Q_f(MF)$$

where $D(MF)$ = the dissociation energy of the alkali-metal fluoride to normal atoms, $L(MF)$ = the heat of sublimation of the fluoride, $Q_f(MF)$ = the heat of formation of the fluoride, and $L(M)$ = the heat of sublimation of the alkali metal, all these quantities referring to 18°.

In this way Barrow and Caunt arrive at the figure $D(F_2) = 50 \pm 6$ kcals., the two fluorides giving results in close agreement. Although little uncertainty attaches to the $Q_f(MF)$ and $L(M)$ values, this is not so for $L(MF)$, for which the correction to 18° requires an extrapolation over an extremely wide temperature range (>1000°). It is not improbable that in this way a considerable error of the same sign and nearly the same magnitude for the two fluorides can enter into the calculations. Barrow and Caunt point out that the greatest uncertainty lies in this $L(MF)$ term and they conclude that a precise value for $D(F_2)$ cannot be obtained in this way, until accurate values for $L(MF)$ are available. Caunt and Barrow (17) have also used a similar cycle involving thallous fluoride and arrived at the result $D(F_2) < 45$ kcals.

When the *available experimental* data are considered as a whole it is clear that an accurate value for $D(F_2)$ which can be accepted with confidence is not yet available. However, we are of the opinion that on the basis of the existing experimental data and the interpretation of these data the value of $D(F_2)$ must lie somewhere in the range :

$$D(F_2) = 37 \pm 8 \text{ kcals. per g.-mol.}$$

Some consequences of a change in the value for $D(F_2)$.

The Thermal Dissociation of F_2.—Wicke (15) has objected to the value of ~33 kcals. for $D(F_2)$ suggested by Schmitz and Schumacher (4). He has pointed out that this low value would demand an appreciable degree of dissociation of fluorine molecules at ~1000°. In a recent paper (16) he has described some thermal conductivity experiments from which he concludes that the percentage dissociation of fluorine is negligible up to 1000° and that $D(F_2)$ cannot lie in the range 30—40 kcals.

Wicke's experiments consisted of a comparison of the thermal conductivities of F_2 and N_2 over a temperature range of 100—1000°, a nickel wire coated with nickel fluoride being used. Within an experimental error of $\pm 10\%$ the thermal conductivities of F_2 and N_2 were found to be the same. Hence Wicke concluded that fluorine is not appreciably dissociated even at 1000°.

Clearly, the main difficulty in experiments of this kind is to prevent attack of the nickel wire during the measurements. This is accentuated, in this case, by the extreme reactivity of fluorine. The attack, even if not sufficiently rapid to destroy the wire quickly, would introduce an exothermic heat term which would tend to mask the effect produced by dissociation. In using this method to distinguish between dissociation energy values it is the measurements in the higher regions of temperature which are clearly of the greatest importance. Such temperature regions, however, involve the greatest likelihood of attack on the wire. From the details given in Wicke's paper, we are not convinced that in this important temperature range attack on the wire by the fluorine is definitely excluded.

The nickel wire was coated by previous exposure to fluorine at red heat (presumably ~700°). There is no evidence presented which shows that this attack by fluorine definitely comes to an end, *i.e.*, that the coating completely protects the wire from further slow attack. Also, the wire was used for measurements at temperatures up to 300° *higher* than that use for the coating process. Further, Wicke states that above 1000° the wire " burnt through." This is certainly due to attack by fluorine since the melting point of nickel is ~1450°. The strongest indication that this coated nickel wire was unreliable is that Wicke could not obtain satisfactory results

with it in experiments with bromine at high temperatures. It is stated that the nickel wire, both uncoated and coated with nickel fluoride, was not stable. Only by using a platinum wire at 800° in the same apparatus was the thermal conductivity observed which corresponded to the expected degree of dissociation.

Wicke and Schäfer (14) have carried out similar thermal conductivity measurements with ClF_3 using a nickel wire. They have obtained values of the equilibrium constant for $ClF_3 \rightleftharpoons ClF + F_2$ which are in agreement with those obtained by other methods. We have already referred to their estimate of the heat of this reaction. However, it is important to note that in these latter experiments the temperature of the wire did *not exceed* 460°. The possibility of attack of the wire is clearly very much less in this case.

We have calculated the equilibrium constant K_c and the percentage dissociation for $F_2 \rightleftharpoons F + F$ at various temperatures and two widely different initial fluorine pressures. The following well-known expression has been used:

$$K_c = \frac{(C_F)^2}{(C_{F_2})} = \frac{\frac{1}{N_0}\left[\frac{(2\pi mkT)^{3/2}}{h^3}\right]^2 v_F v_F^2 h^3}{\frac{(2\pi \cdot 2mkT)^{3/2}}{h^3} \cdot v_{F_2} 8\pi^2 AkT \cdot f(v)_{F_2}} \cdot e^{-E/RT}$$

in which C_F and C_{F_2} are concentrations in moles c.c.$^{-1}$, m = the mass of the fluorine atom in g., k = Boltzman's constant, h = Planck's constant, T = absolute temperature. σ_{F_2} = the symmetry number of F_2 (= 2), v_F = the electronic partition function for fluorine atoms, v_{F_2} = the electronic partition function for F_2 (= 1), A = the moment of inertia of F_2, E = the dissociation energy of the fluorine molecule, and $f(v)_{F_2}$ = the vibrational partition function of F_2.

The fundamental frequency of vibration, ν_0, of F_2 in the expression $f(v)_{F_2} = \left[1 - e^{-\frac{h\nu_0}{kT}}\right]^{-1}$, is not known.* We have estimated it by assuming that the restoring force constant for F_2 is the same as that for I_2. In the above expression for K_c, two different values of E, *viz.*, 37 and 45 kcals. have been used; the latter corresponds to the highest value of $D(F_2)$ which we consider possible. The results are given in Table II; P_{F_2} is the initial pressure of fluorine.

TABLE II.

	E = 37 kcals.			E = 45 kcals.		
		P_{F_2} = 380 mm.	$P_{F_2} = 10^{-3}$ mm.		P_{F_2} = 380 mm.	$P_{F_2} = 10^{-3}$ mm.
Absolute temperature.	K_c.	Dissociation, %.		K_c.	Dissociation, %.	
1273	$5{\cdot}11 \times 10^{-4}$	40	100	$2{\cdot}19 \times 10^{-3}$	10·2	100
1073	$3{\cdot}39 \times 10^{-5}$	11·5	100	$0{\cdot}82 \times 10^{-4}$	1·9	93·5
873	$6{\cdot}37 \times 10^{-6}$	1·5	90·5	$0{\cdot}66 \times 10^{-5}$	—	25·7

The values of the percentage dissociation given in Table II indicate that it might be possible to make a direct determination of $D(F_2)$ by measuring the temperature coefficient of the equilibrium constant for $F_2 \rightleftharpoons 2F$. Under certain conditions the dissociation is very marked and should be easily measurable, apart, of course, from serious technical difficulties arising from the great reactivity of fluorine.

Bond Dissociation Energies of the Halogens and of Molecules isoelectronic with Fluorine.—The old value of $D(F_2) = 63{\cdot}5$ kcals. leads to a monotonous decrease in the dissociation energy of the halogen molecules along the series F_2 to I_2. Within the range of values 37 ± 8 kcals. this decrease no longer occurs; the dissociation energies show a maximum at chlorine. This feature, if it is established, might be understood in the following way. In Mulliken's terminology, the classification of the orbitals of the fourteen electrons, which derive from the outer s and p electrons of the two separate halogen atoms, is the same except for a progressive increase in principal quantum number from fluorine to iodine. The classification is

$$(s\sigma)^2(ys)^2(s\sigma)^2(u\pi)^4(v\pi)^4$$

The $(s\sigma)^2$, $(s\sigma)^2$ and $(u\pi)^4$ electrons are bonding, and the $(ys)^2$ and $(v\pi)^4$ electrons are anti-bonding. On this basis, a monotonous gradation in dissociation energy might be expected since the binding energy of the bonding electrons would decrease with increasing principal quantum number and increasing screening power of the inner shells. However, from Cl_2 to I_2 an additional

* *Added in proof.* Since this paper was submitted for publication an experimental value for ν_0 has become available. This gives K_c values which are about 30% higher than those shown in Table II and, consequently, slightly larger values for the percentage dissociation.

factor can operate. There may be a certain degree of hybridization between p and d orbitals of the *same* principal quantum number in the case of the valence electrons of the separated atoms. This would increase the bonding power and decrease the anti-bonding power of these electrons. The degree of hybridisation would increase from Cl_2 to I_2, but, of course, in this sequence other factors supervene and cause an overall decrease in the bond energy from Cl_2 to I_2. In fluorine, however, a different situation may well arise because the atom possesses no d orbitals of the same principal quantum number and hence there can be no hybridisation offsetting the anti-bonding power of the p electrons.

We have also considered the possibility of understanding this maximum in the bond energies of this series in terms of resonance between covalent and ionic structures, *viz.*, X : X and X^+X^-. The energy of separation between the covalent and the ionic structures will be markedly larger for F_2 than for the rest of the halogens, on account of the extremely high ionisation potential of fluorine. Thus a sequence of increasing values of the ionic resonance energy, together with a sequence of decreasing pure covalent-bond energies, might result in a maximum binding energy at chlorine. However, it is found that this demands a value for the resonance energy in the case of chlorine which is improbably large.

There is another trend of bond dissociation energies which is of some interest, *viz.*, that in the sequence along the first row of the Periodic Table. The data are :

Molecule	C_2H_6	N_2H_4	H_2O_2	F_2
Bond	C–C	N–N	O–O	F–F
Dissociation energy, kcals.	86 [a]	60 ± 3 [b]	53·6 [c]	37 ± 8 (63·5)

[a] Taken from the Table given by Steacie, "Atomic and Free Radical Reactions," New York, 1946. [b] Szwarc, *Proc. Roy. Soc.*, 1949, *A*, **198**, 267. [c] From $Q_f(H_2O_2)$ and $D(O\text{–}H) = 101$ kcals.; Gaydon (8).

It is seen that, with our suggested range for $D(F_2)$, the above trend is monotonous, whereas this is not the case if $D(F_2) = 63{\cdot}5$ kcals. We feel that this steady decrease in dissociation energy is of more significance that the sequence $F_2 \longrightarrow I_2$, since, as we have already indicated, there are grounds for the belief that the $F_2 \longrightarrow I_2$ trend should not necessarily be monotonous.

The thermochemistry of reactions involving fluorine. A change of $\Delta D(F_2)$ in the value for the dissociation energy of fluorine will produce a change of $\frac{1}{2}\Delta D(F_2)$ per F atom in Q_a, the heat of formation of a fluoride from gaseous atoms. Hence, estimates from heats of formation of the dissociation energies of single bonds to fluorine atoms will be altered by $\frac{1}{2}\Delta D(F_2)$; *e.g.*,

$$D(R\text{–}F) = Q_a(R\text{–}F) - Q_a(R)$$

This change of $\frac{1}{2}\Delta D(F_2)$ also applies to estimates of " average bond energies " or " bond energy terms " in a polyatomic molecule. On the other hand, Q_f values for fluorides, *i.e.*, heats of formation of the compounds from the elements *in their standard states*, are clearly independent of $D(F_2)$. There are various simple processes of interest, the heats of which are independent of changes in $D(F_2)$:

(1) $F_2(g) + H_2(g) \longrightarrow 2HF(g)$
(2) $RH + F_2 \longrightarrow RF + HF$
(3) $R_1{\cdot}CH_2{\cdot}CH_2{\cdot}F \longrightarrow R_1{\cdot}CH{:}CH_2 + HF$
(4) $e^- + RF \longrightarrow R + F^-$

A change of $\Delta D(F_2)$ in $D(F_2)$ produces a change of $\frac{1}{2}\Delta D(F_2)$ in $D(RF)$ and, as will be seen from a later section of this paper, an exactly offsetting change in E_y, the electron affinity of a gaseous fluorine atom.

(5) The sodium " flame " reaction,

$$(Na)_y + (RF)_y \longrightarrow (Na^+F^-)_y + R{\cdot},$$

In contrast to the above examples, in a reaction system which contains fluorine molecules any considerations concerning the possible rôle played by the dissociation $F_2 \longrightarrow 2F$ will be affected by the value of $D(F_2)$ adopted. Also the heats of reactions of the type,

$$F_2 + A \longrightarrow F + F\text{–}A$$

in which A is a molecule or radical, will be altered by $\frac{1}{2}\Delta D(F_2)$. Examples of interest are :

$$H + F_2 \longrightarrow HF + F$$
$$R{\cdot} + F_2 \longrightarrow RF + F$$
$$F_2 + CH_2{:}CHR \longrightarrow F{\cdot}CH_2{\cdot}CHR\text{–} + F$$

A striking consequence of our conclusion that $D(F_2) < 45$ kcals. is that the value of the electron affinity of a gaseous fluorine atom, derived by means of the Born–Haber cycle, is not greater than, and probably *less* than, that of chlorine. This is discussed fully in the next section.

The Electron Affinity of Fluorine.—For an alkali-metal halide MX, the Born–Haber cycle leads to the expression :

$$E_a = Q(MX)_c + S(M)_a + I(M) + \tfrac{1}{2}D(X_2) + U_c$$

in which E_a = the electron affinity of the gaseous halogen atom, $Q(MX)_c$ = the heat of formation of crystalline MX from $(M)_c$ and *gaseous* X_2, $S(M)_a$ = the heat of sublimation of the alkali metal, $I(M)$ = the ionisation potential of the alkali-metal atom, $D(X_2)$ = the dissociation energy of the halogen molecule, and U_c = the lattice energy of crystalline MX.

Using this method, Sherman (18) found the following electron affinity values :

F, 98·5; Cl, 92·5; Br, 87·1; I, 79·2.

Mayer and Helmholtz (19), using a different form for the ionic interaction energy, found :

F, 95·3; Cl, 86·5; Br, 81·5; I, 74·2.

Both these values for E_a are based on $D(F_2) = 63{\cdot}5$ kcals. It is clear that values of $D(F_2)$ in the range 37 ± 8 would reduce the above figures by $13{\cdot}2 \pm 4$ kcals., to values which are less than the corresponding chlorine figures. This consequence has already been pointed out by Wicke (15), who uses it as an argument against a low value of $D(F_2)$. We do not consider the argument acceptable. We have first examined the data used in the cycle to see if there are any uncertainties which may be sufficiently large to permit the conclusion that E_a could be greater than E_{Cl}, even with a low value for $D(F_2)$ in the range suggested above.

Table III [taken from Rice (20)] is a typical presentation of the data used in the calculation of electron affinities. The lattice energies are the values obtained by Huggins (21), who has carried out the most comprehensive calculations of these quantities, corrected to room temperature. The remaining data are taken from Rossini and Bichowski (13). We have used our suggested range for the quantity $D(F_2)$.

The most striking feature of Table III is the relatively small variation in the different E_a

TABLE III.

Salt.	$Q(MX)_c$.	$S(M)_a$.	$I(M)$.	$\frac{1}{2}D(X_2)$.	$-U_c$.	E_a.	Average E_a.	E_a (exptl.).
LiF	145·6	39·0	123·8	18·5 ± 4	245·1	81·8 ± 4		
NaF	136·0	25·9	118·0	"	216·4	82·0 ± 4		
KF	134·5	19·8	99·7	"	193·2	79·3 ± 4	81·7 ± 4	
RbF	133·2	18·9	95·9	"	183·4	83·1 ± 4		
CsF	131·7	18·8	89·4	"	175·9	82·5 ± 4		
LiCl	97·6	39·0	123·8	28·9	201·1	88·2		86·6 [a], 92·7 [b]
NaCl ...	98·3	25·9	118·0	28·9	184·0	87·1		85·8 [c], 85·5 [d]
KCl	104·4	19·8	99·7	28·9	168·3	84·5	87·3	87·1 [d]
RbCl ...	105·1	18·9	95·9	28·9	162·1	86·7		
CsCl	106·3	18·8	89·4	28·9	153·2	90·2		
LiBr	87·6	39·0	123·8	23·1	189·9	83·6		86·5 [a]
NaBr ...	90·6	25·9	118·0	23·1	175·9	81·7		87·5 ± 4·6 [f]
KBr	97·9	19·8	99·7	23·1	161·5	79·0	81·8	88 ± 3·4 [e]
RbBr ...	99·6	18·9	95·9	23·1	156·1	81·4		80·5 ± 0·4 [h]
CsBr ...	101·5	18·8	89·4	23·1	149·6	83·2		83·9 [d]
LiI	72·5	39·0	123·8	18·1	176·2	77·2		74·6 [i], 72·4 [f]
NaI	76·7	25·9	118·0	18·1	164·4	74·3		72·6 [h], 76·3 [i]
KI	86·3	19·8	99·7	18·1	152·5	71·4	74·3	
RbI	88·5	18·9	95·9	18·1	147·9	73·5		
CsI	91·4	18·8	89·4	18·1	142·4	75·3		

[a] Saha and Tandon, *Proc. Nat. Inst. Sci. India*, 1937, **3**, 287, 296. [b] Mayer and Mitchell, *J. Chem. Physics*, 1940, **8**, 85, 282. [c] Mayer and McCallum, *ibid.*, 1943, **11**, 56. [d] Ionov, *Compt. rend. Acad. Sci. U.S.S.R.*, 1940, **28**, 512. [e] Piccardi, *Atti R. Accad. Lincei*, [vi], 1926, **3**, 566. [f] Blewett, *Physical Rev.*, 1936, **49**, 900. [g] Glockler and Calvin, *J. Chem. Physics*, 1936, **4**, 492. [h] Doty and Mayer, *ibid.*, 1944, **12**, 323. [i] Glockler and Calvin, *ibid.*, 1935, **3**, 771. [j] Mayer and Sutton, *ibid.*, p. 20. [k] *Idem*, *ibid.*, 1934, **2**, 146. [l] Ionov, *J. Exp. Theor. Phys. U.S.S.R.*, 1940, **10**, 1248.

values for a given halogen, and for Cl, Br, and I the satisfactory agreement between the mean of the calculated and experimental values. This indicates that, if there are any uncertainties in the data, they cannot be haphazard experimental errors but must have very special regularities and more or less cancel out in the case of the Cl, Br, and I cycles. Also in order to offset the decrease in E_γ due to the lower value of $D(F_2)$, the errors should combine in such a way that the revised E_γ values, derived from the different alkali-metal cases, are in reasonable agreement. For example, the complete neglect of any covalent character in the binding energy of the lattice might be considered to introduce errors.

The quantities I(M) and S(M) are open to little error, particularly the former. Moreover, the agreement in the five calculated values of E_γ for each halogen demands that any errors in one or both of the terms I(M) and S(M) would have to be *the same for each alkali metal*. This can be ruled out. Similar considerations apply to Q_f(MX) for each alkali-metal halide. Further, it should be noted that von Wartenberg (12) and Schmitz and Schumacher (4) have independently determined $Q_f(NaF)_g - Q_f(NaCl)_g$ by a direct method, obtaining results in good agreement with the difference in the values given in Table III, which have been obtained separately by indirect methods. It seems extremely unlikely that this agreement would be obtained if there were any relatively large errors in the Q_f values for alkali-metal fluorides and chlorides.

There remains for consideration the lattice energy term. We have compared the calculated values of lattice energies from the following sources: Sherman (18), Mayer and Helmholtz (19), Huggins (21), Verwey and de Boer (22), Rice (20), and Slater (23). The underlying principles are the same in all cases but the methods vary in the details of the expressions used for the potential energy of the ionic crystals. In spite of such differences, the calculated values agree remarkably well amongst themselves and with the experimental values available. The largest divergence is about 5% in the worst cases but most of the deviations are less than this. What is more important for our considerations of E_γ relative to E_{Cl} is that the variations in U_0(MF) $-$ U_0(MCl), with the different methods, are still less—on the average 2 kcals., and never greater than 3 kcals.

This agreement in calculated values for lattice energies can be understood from the following simplified considerations. There are two widely used expressions for the potential energy of a crystal lattice in terms of attraction- and repulsion-energy terms. Simple forms of these are:

$$U_0 = -\frac{Ae^2}{r_0}\left(1 - \frac{1}{n}\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$U_0 = -\frac{Ae^2}{r_0}\left(1 - \frac{\rho}{r_0}\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

in which A is the Madelung constant, r_0 is the equilibrium interionic distance between nearest neighbours, and n and ρ are constants.

The constants n and ρ may be evaluated by relating d^2U_r/dV^2 to the compressibility of the crystal. In equations (2) and (3), the magnitudes of n and ρ are such that the second term is relatively small, so that the calculated values of U_0 are very insensitive to changes in the values of n and ρ. It can be seen that the methods of calculation of U_0 are all self-compensatory in the sense that, if an extra term is added to the potential-energy expression (*e.g.*, a van der Waals attraction term), then the use of the condition $(dU/dV)_{r_0} = 0$ and the evaluation of n and ρ from the relation between d^2U/dV^2 and the compressibility will compensate for this new term, through an inevitable change in the repulsion term. The critical parameter in these calculations is r_0, and the values of this are known very accurately for the alkali-metal halides. We are of the opinion that, unless the generally accepted principles underlying lattice-energy calculations are abandoned for a completely new approach, any serious revision of U_0 values, particularly of the kind which would render $E_\gamma > E_{Cl}$, is very unlikely.

We consider that this examination of the Born–Haber cycle leads inescapably to the conclusion that if $D(F_2)$ lies in the range 37 ± 8 kcals., the electron affinity of a gaseous fluorine atom cannot be greater than, and is very probably less than, that for chlorine.

The Electron Affinity of Fluorine in Aqueous Solution.—The work of M. G. Evans and his collaborators (24) on oxidation–reduction reactions has emphasised the importance of a quantity which may be termed the solution electron affinity of a radical. This quantity is the sum of the electron affinity of the gaseous atom or radical and the heat of solution of the corresponding negative ion, *i.e.*, $E + H_s$. The difference between $E + H_s$ values for two radicals may be very different from the difference between the electron affinities of the gaseous radicals. For example $E_{Cl} - E_{OH} \approx 40$ kcals., whereas $(E + H_s)_{Cl} - (E + H_s)_{OH} \approx 3$ kcals. It is of some

interest to examine the situation with regard to fluorine. Differences in $(E + H_s)$ values can be derived from the equations :

$$M_s + \tfrac{1}{2}(X_2)_s \longrightarrow M^+_{aq} + X^-_{aq} \quad \ldots\ldots \quad Q_f(MX)_{aq} \quad \ldots\ldots \quad (4)$$

$$M_s + \tfrac{1}{2}(Y_2)_s \longrightarrow M^+_{aq} + Y^-_{aq} \quad \ldots\ldots \quad Q_f(MY)_{aq} \quad \ldots\ldots \quad (5)$$

$$\tfrac{1}{2}(Y_2)_s \longrightarrow (Y)_g \quad \ldots\ldots \quad \tfrac{1}{2}Q_f(Y)_g \quad \ldots\ldots \quad (6)$$

$$(X)_g \longrightarrow \tfrac{1}{2}(X_2)_s \quad \ldots\ldots \quad -\tfrac{1}{2}Q_f(X)_g \quad \ldots\ldots \quad (7)$$

in which M is an alkali metal, and X and Y are halogens, the suffix s denoting the halogen molecules in their *standard states*. Equation (4) − (5) + (6) + (7) gives :

$$(X)_g + Y^-_{aq} \longrightarrow X^-_{aq} + (Y)_g \quad \ldots \quad [Q_f(MX)_{aq} - \tfrac{1}{2}Q_f(X_2)_s] - [Q_f(MY)_{aq} - \tfrac{1}{2}Q_f(Y_2)_s]$$

It is clear that the heat of this reaction is the difference in the $(E + H_s)$ values for the two halogens, *i.e.*, $\Delta(E + H_s)(X/Y)$. These differences have been calculated for the four halogens from the data given by Rossini and Bichowski (13) for the alkali-metal salts. The mean values are :

	F/Cl.	Cl/Br.	Br/I.
$\Delta(E + H_s)$	24·1—32·1	13·0	16·6

The F/Cl value is based on $D(F_2) = 37 \pm 8$ kcals. It is seen that $(E + H_s)_F > (E + H_s)_{Cl}$ in spite of the fact that $E_F < E_{Cl}$. This is clearly because the smaller fluorine ion has a much higher heat of solution than the chloride ion. $(H_s)_F - (H_s)_{Cl}$ is positive and larger in magnitude than $E_F - E_{Cl}$. To illustrate this we have calculated ΔH_s values for the pairs of halogen atoms. It can easily be shown that

$$H_s(X) - H_s(Y) = [U_s(MX)_c - L(MX)_c] - [U_s(MY)_c - L(MY)_c]$$

in which $L(MX)_c$ and $L(MY)_c$ are the heats of solution of the crystalline alkali-metal halides MX and MY. A table of U_0 and L values is given by Rice (20). Mean values of ΔH_s from the data for the alkali-metal halides are :

	F/Cl.	Cl/Br.	Br/I.
ΔH_s	33·8	7·4	9·3

ΔH_s(F/Cl) is seen to be more positive than $\Delta(E + H_s)$(F/Cl).

The Ionic Character of Covalent Bonds involving Fluorine Atoms.—The concept of covalent bonds with partial ionic character, as developed by Pauling (25), is well known. In many cases it is useful to describe the bond between two centres, say A and F, in terms of resonance between two structures A:F, in which A and F are linked by a pure covalent bond, and A^+F^-, in which A and F are linked by a pure electrovalency. The alternative ionic structure A^-F^+ can usually be neglected from energy considerations. If ϕ_c and ϕ_i are the wave functions for the covalent and the ionic structures, respectively, then $a_c\phi_c + a_i\phi_i$ is an approximation for the wave function for the actual state of the molecule AF. The coefficients a_c and a_i have values which minimise the energy. The percentage ionic character of the bond A–F is usually defined as $100a_i^2$.

If, at the normal internuclear separation of the bond A–F, the potential energies of the actual state of the molecule, the pure covalent structure, and the ionic structure are V_a, V_c, and V_i, respectively, then it can be shown that

$$a_i^2 \approx \frac{R}{2R + S}$$

in which $R = (V_c - V_a)$ is the resonance energy relative to the pure covalent structure and $S = (V_i - V_c)$ is the energy of separation between the pure covalent and the pure ionic structures. The potential energies V_a, V_c, and V_i all refer to the zero corresponding to dissociation into normal atoms or radicals, $A + F$. If V_{ii} is the potential energy of the ionic structure relative to the zero $A^+ + F^-$, then $V_i = V_{ii} + I_A - E_F$, and $S = V_{ii} + I_A - E_F - V_c$.

Consider the effect of a change of $\Delta D(F_2)$ in the value for the dissociation of fluorine on the percentage ionic character of an A–F bond. If V_a, which is negative, is determined from heats of formation, then it becomes $V_a' = V_a - \frac{1}{2}\Delta D(F_2)$. Pauling has suggested the empirical arithmetic mean rule for evaluating V_c, *viz.* :

$$V_c = -\tfrac{1}{2}[D(A\text{–}A) + D(F\text{–}F)]$$

V_c is negative, whereas D(A–A) and D(F–F) are usually taken as positive. On this basis V_c becomes $V_c' = V_c - \frac{1}{2}\Delta D(F_2)$. We have shown above that this change of $\Delta D(F_2)$ alters the

electron affinity of fluorine by $\frac{1}{2}\Delta D(F_2)$. Hence V_i becomes $V_i' = V_i - \frac{1}{2}\Delta D(F_2)$. Substituting the new values V_a', V_c' and V_i' in the expressions for R and S shows that the values of these quantities remain unaltered. Hence the percentage ionic character is unchanged. Previously, simple calculations of ionic character on the above lines using $D(F_2) = 63{\cdot}5$ kcals. had led to the view that the ionic resonance energy and ionic character of H–F and C–F bonds was larger than that of the corresponding bonds for the remaining halogens. This view requires no revision if $D(F_2)$, and consequently E_R, are altered.

Incidentally, it is of interest to note that the relatively large ionic character of C–F and H–F bonds is not due to the higher electron affinity of fluorine. It is mainly due to the internuclear separations of these bonds being smaller than those involving the other halogens. This factor gives rise to smaller values of S and larger negative values for the so-called resonance integral, and hence to larger values of R. If Pauling's geometric mean rule is adopted for the evaluation of V_c, then changing $D(F_2)$ by $\Delta D(F_2)$ alters V_i by an amount which is not exactly $\frac{1}{2}\Delta D(F_2)$. This causes slight changes in R, S, and a_i^2. However, these differences are too small to be of any significance.

We have concluded that the existing experimental data indicate strongly that the dissociation energy of fluorine and the electron affinity of a gaseous fluorine atom are less than the corresponding quantities for chlorine. This may, at first sight, appear surprising. It is, therefore, of interest to note that there is evidence which points to the existence of the same situation for oxygen and sulphur.

To illustrate this we have collected the relevant data in Table IV. Two sets of data are presented for sulphur, since there are two alternative values for $D(S_2)$. The column labelled *H*

TABLE IV.

Sulphur. Property.	Value. *H.*	Value. *G.*	Oxygen. Property.	Value
$Q_f(S)_g$	−56·1	−65·1	$Q_f(O)_g$	−59·1
D(H–S·)	78·9	83·4	D(H–O·)	101
Q_f(HS·)	−29·0	−33·5	Q_f(HO·)	−10·0
E_{ss}	59·3	63·8	E_{oo}	51·7 (40*)
D(S–S) in H_2S_2	49·1	58·1	D(O–O) in H_2O_2	53·6
D(S–S) in S_8	>53·4	>62·4		

All energies are given in kcals.
* Value for E_{oo} derived by Baughan, Evans, and Polanyi (*Trans. Faraday Soc.*, 1941, **37**, 377).

gives data based on $D(S_2) = 83$ kcals. [Herzberg] (26), that labelled *G* is based on $D(S_2) = 101$ kcals. [Gaydon] (8). Unfortunately, there is no experimental value for D(H–S·) for the HS· radical. This quantity is required for the evaluation of Q_f(HS·), E_{ss}, and D(S–S) in H_2S_2. The values for D(H–S·) given in the Table are based on the following considerations. D(H–O·) = 101 kcals., which is well established, is about 9 kcals. less than the average O–H bond energy in H_2O, *i.e.*, $Q_a(H_2O)/2$. There is evidence that D(H–N) is about 6 kcals. less than $Q_a(NH_3)/3$. Since sulphur is even less electronegative than nitrogen we have concluded that the difference between $Q_a(H_2S)/2$ and D(H–S·) will be even less and have taken this difference to be about 3·5 kcals. The values of E_{ss} have been calculated from the lattice energies of NaHS and KHS given by West (27), who obtained a value for E_{ss} (61 kcals.) very close to those given in the table. The value of E_{oo} is the mean of values calculated from the lattice energies of the alkali-metal hydroxides given by Goubeau and Klemm (28). These authors give a mean value for E_{oo} of 48 kcals. The figures given for D(S–S) in S_8 are obtained from $Q_a(S_2)_g/8$; we consider that the dissociation energy of one S–S bond in this ring will certainly be somewhat greater than these average values.

It is seen that, independently of the uncertainty in $D(S_2)$, the electron affinity of the HS· radical is larger than that of the HO· radical. On the whole, the bond-energy data indicate that the dissociation energy of an S–S single bond is probably a little larger than that of an O–O single bond.

Thus it seems fairly conclusive that the surprising feature of the trends in dissociation energy and electron affinity in the halogen series which arises from the acceptance of a low value for $D(F_2)$ and have sometimes been regarded as evidence against such a value, is not, in fact, unique. Similar trends are shown by oxygen and sulphur.

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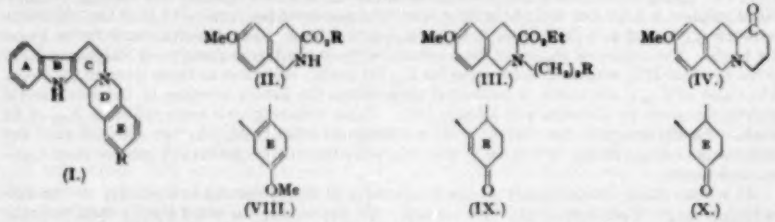
318. *The Constitution of Yohimbine and Related Alkaloids. Part IV. A Synthesis of Yohimbone.*

By G. A. SWAN.

A compound having the structure (I; R = OMe) has been synthesised by two independent methods. By reduction of this with sodium and *tert.*-butanol in liquid ammonia and treatment of the product with acid, followed by catalytic hydrogenation, a racemic base (X) has been obtained. Resolution of this gave a (−)-base, identical with yohimbone.

THE present paper describes experiments which have been carried out to synthesise yohimbone, the Oppenauer oxidation product of yohimbine (Witkop, *Annalen*, 1943, **554**, 83), bearing in mind the future extension to the synthesis of yohimbine itself.



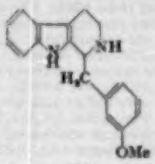
The synthesis of (I; R = H) has already been described (Part I, *J.*, 1946, 617; Part III, *J.*, 1949, 1720) and that of (I; R = OMe) is now recorded. Earlier work resulted in the preparation of this compound by an extension of the method described for (I) in Part I; although the yield was low, it appeared possible to use a similar route to obtain a product in which ring E was hydrogenated. *m*-Methoxyphenylalanine was condensed with formaldehyde in alkaline solution at 37° to give 6-methoxy-1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylic acid (II; R = H) (the strongly acidic conditions used in Part I are unsuitable on account of the possibility of hydrolysis of the methoxyl group). The ethyl ester (II; R = Et) was condensed with

γ-bromobutyronitrile to give ethyl 6-methoxy-2-3′-cyanopropyl-1 : 2 : 3 : 4-tetrahydroisoquinoline-3-carboxylate (III; R = CN) which was converted into ethyl 6-methoxy-2-3′-carbethoxypropyl-1 : 2 : 3 : 4-tetrahydroisoquinoline-3-carboxylate (III; R = CO_2Et). This diester was subjected to the Dieckmann reaction, giving 9-keto-2′-methoxy-1 : 4 : 6 : 7 : 8 : 9-hexahydro-2 : 3-benzpyridocoline (IV), the phenylhydrazone of which underwent the Fischer indole reaction giving 3″-methoxy-3 : 4 : 6 : 9-tetrahydro-7 : 8-benzindolo(2′ : 3′-1 : 2)-pyridocoline (I; R = OMe).

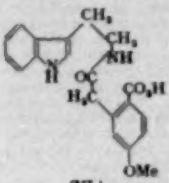
The dehydrogenation of ethyl 1 : 2 : 3 : 4-tetrahydroisoquinoline-3-carboxylate with sulphur in tetralin (cf. G.P. 674,400) gave ethyl *iso*quinoline-3-carboxylate. In a similar manner, ethyl 6-methoxyisoquinoline-3-carboxylate was prepared.

It was hoped that a more convenient synthesis of (I; R = OMe) would be the methylation of (I; R = OH), obtained by the condensation of *m*-hydroxyphenylpyruvic acid with tryptamine, and cyclisation of the product with formaldehyde (Hahn and Hansel, *Ber.*, **1938**, **71**, 2194). Unfortunately attempted methylation (*e.g.*, with diazomethane in ether–methanol or ether–dioxan) gave only traces of the required product. The preparation of *m*-hydroxyphenylpyruvic acid by Hahn and Werner's method (*Annalen*, **1935**, **520**, 130) gives poor yields; by the use of aceturic acid in place of hippuric acid (cf. MacDonald, *J.*, 1948, 376), α-acetamido-*m*-acetoxycinnamic acid azlactone was obtained in 62% yield, and this was hydrolysed to *m*-hydroxyphenylpyruvic acid in 75% yield. In contrast, for the preparation of *m*-methoxyphenylpyruvic acid (see below), the azlactone derived from *m*-methoxybenzaldehyde and hippuric acid (Pschorr, *Annalen*, **1912**, **391**, 44) was preferred to α-acetamido-*m*-methoxycinnamic acid azlactone, as the latter could be obtained only in low yield by the aceturic acid condensation.

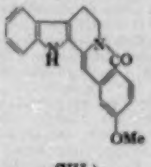
Finally, a convenient synthesis of (I; R = OMe) was found in the condensation of *m*-methoxyphenylpyruvic acid with tryptamine to give 2-*m*-methoxybenzyl-2 : 3 : 4 : 5-tetrahydro-β-carboline (V) followed by reaction with formaldehyde in aqueous solution at 40—45°.



(V.)



(VI.)



(VII.)

In another possible route to (I; R = OMe), tryptamine was condensed with 5-methoxybromophthalic anhydride (obtained by the action of acetyl chloride on the acid) to give *N*-2′-3″-indolylethyl-2-carboxy-5-methoxyphenylacetamide (VI). This was esterified with diazomethane and the product treated with phosphoryl chloride in an attempt to prepare (VII); but only a very small amount of what appeared to be the required product was isolated. Further attempts to convert (VII) into (I; R = OMe) by reduction first with lithium aluminium hydride, then catalytically, were therefore abandoned.

With a view to the synthesis of derivatives of (I; R = OMe) in which ring E is hydrogenated, attempts were made to hydrogenate (II; R = Et) to ethyl 6-methoxydecahydroisoquinoline-3-carboxylate; but difficulty was experienced in preventing further action on the carbethoxy-group. Hydrogenation could be accomplished in acetic acid solution with platinum at 6 atmospheres' pressure; or in ethanol with nickel on kieselguhr (Covert, Connor, and Adkins, *J. Amer. Chem. Soc.*, **1932**, **54**, 1651) at 155—160° and 80 atmospheres. The latter catalyst is already known to be preferable to Raney nickel for the hydrogenation of anisole derivatives, as it is less liable to cause hydrogenolysis of the ether linkage (Duzee and Adkins, *J. Amer. Chem. Soc.*, **1935**, **57**, 147). The reduced ester was treated as for the conversion of (II; R = Et) into (IV), and gave a gum which was probably a mixture of stereoisomeric forms of (IV) in which the benzene ring is hydrogenated; but no crystalline derivatives could be obtained.

The hydrogenation of the ketone (IV) has also been investigated. With platinum and acetic acid at room temperature and atmospheric pressure, 1 mol. of hydrogen was rapidly absorbed, and from the product two crystalline compounds, ' base *A* ' and ' base *B*,' were isolated. The analytical results agreed with the empirical formula $C_{14}H_{15}O_2N$ in each case, suggesting that these were the two possible racemic forms of (IV; CH·OH instead of CO). The same products

were also obtained by the Ponndorf–Meerwein reduction of (IV). The acetylated bases *A* and *B* (prepared by using acetic anhydride) had the empirical formula $C_{14}H_{21}O_3N$. Attempts to oxidise the bases back to the original ketone by chromic acid, the Oppenauer method (by using aluminium phenoxide and *cyclo*hexanone in xylene), or the modification of the latter due to Woodward, Wendler, and Brutschy (*J. Amer. Chem. Soc.*, 1945, **67**, 1425) failed.

Finally, a successful synthesis of yohimbone was achieved by the following process in which the asymmetric centres are introduced one at a time so that at no stage should more than two racemates be produced. The compound (I; R = OMe) was reduced to ' base *C*,' presumably 3''-methoxy-3 : 4 : 6 : 9 : 1'' : 4''-hexahydro-7 : 8-benzindolo-(2' : 3'-1 : 2)pyridocoline (VIII), by the action of sodium and *tert.*-butanol in liquid ammonia (cf. Birch, *J.*, 1944, 430). When ' base *C* ' was treated with aqueous methanolic hydrochloric acid, it yielded ' base *D*,' together with a small amount of ' base *E*,' presumably the two racemic forms of (IX). ' Base *D* ' was hydrogenated in the presence of Adams's catalyst in glacial acetic acid; the hydrogen uptake slowed down after the absorption of 1 mole so the hydrogenation was interrupted, and a keto-base, m. p. 266° (decomp.), isolated. This must be the previously unknown (±)-yohimbone as it was resolved through the salt with (−)-camphor-10-sulphonic acid [the (−)-base-(−)-acid salt being the less soluble in ethanol] and the resulting (−)-base, m. p. 305—306° (decomp.), $[\alpha]_D^{18}$ −106°, proved identical with yohimbone obtained from yohimbine by the Oppenauer oxidation. No depression of m. p. was observed on admixture of the two bases or of their methiodides.

Thus structure (X) for yohimbone is considered to be established synthetically, the only uncertain feature being the configurations of the asymmetric centres. This confirms the nuclear structure and the position of the hydroxyl group of yohimbine itself.

Experimental.

Unless otherwise stated, the light petroleum used had b. p. 60—80°. All m. p.s are uncorrected.

*Ethyl iso**Quinoline-3-carboxylate*.—A mixture of ethyl 1 : 2 : 3 : 4-tetrahydroisoquinoline-3-carboxylate (1·2 g.), flowers of sulphur (0·5 g.), and tetralin (4 c.c.) was heated for 4 hours at 160—165°. The cooled product was diluted with benzene, and the filtered solution extracted with dilute hydrochloric acid. The acid extract was basified (sodium carbonate solution) and extracted with ether, the extract dried (K_2CO_3), the ether removed, and the residue distilled, giving a colourless oil (0·5 g.; b. p. 165—170°/2 mm.). This yielded a crude *picrate*, m. p. 154—157°; when recrystallised from ethanol this formed a yellow powder, m. p. 157° (Found: C, 50·25; H, 3·3. $C_{18}H_{16}O_9N_4C_6H_3O_7N_3$ requires C, 50·25; H, 3·25%). The picrate (1 g.) was ground with hydrochloric acid (20%), the resulting picric acid removed by filtration, and the filtrate basified (Na_2CO_3) and extracted with ether. The extract was dried (K_2CO_3), the ether removed, and the *base* (0·3 g.; b. p. 165—170°/2 mm.) distilled as a colourless oil which soon set to a white solid (after being washed with light petroleum) (0·29 g.; m. p. 40—46°) (Found: C, 71·65; H, 5·45. $C_{11}H_{11}O_2N$ requires C, 71·65; H, 5·45%).

α-Acetamido-m-acetoxycinnamic Acid Azlactone.—The temperature of a mixture of *m*-hydroxybenzaldehyde (7·15 g.), aceturic acid (8·1 g.), acetic anhydride (23 c.c.), and triethylamine (6·5 c.c.) was raised from 15° to 70° during 5 days, then kept at 0° for 1 day. The resulting solid was collected, washed with aqueous ethanol, and dried (8·85 g.; m. p. 118—120°). Recrystallised twice from ethanol this afforded the *azlactone* as pale-yellow crystals, m. p. 120—121° (Found: C, 62·5; H, 5·2. $C_{13}H_{11}O_4N,\frac{1}{4}C_2H_4O$ requires C, 62·7; H, 5·2%).

m-Hydroxyphenylpyruvic Acid.—The azlactone (0·9 g.) was heated under reflux for 2½ hours with a mixture of concentrated hydrochloric acid (1·1 c.c.) and water (12 c.c.). The solution was cooled and after the addition of aqueous sodium hydrogen sulphite (40%; 6 c.c.) it was extracted with ether, strongly acidified (concentrated hydrochloric acid) and evaporated (water-bath) to dryness under reduced pressure. The residue was extracted with ethyl acetate, the extract evaporated, and the resulting yellow solid washed with light petroleum, affording the acid (0·5 g.), m. p. 163° (decomp.).

α-Acetamido-m-methoxycinnamic Acid Azlactone.—(*a*) A mixture of *m*-methoxybenzaldehyde (Chakravarti and Nair, *J. Indian Chem. Soc.*, 1932, **9**, 580) (1·02 g.), aceturic acid (0·59 g.), acetic anhydride (1·2 c.c.), and fused sodium acetate (0·3 g.) was heated under reflux for 1 hour, and cooled, and the *azlactone* collected, washed with aqueous ethanol, and dried (0·65 g.; m. p. 99—100°). Recrystallised from ethanol this formed pale yellow crystals, m. p. 103—104° (Found: C, 64·95; H, 5·8. $C_{13}H_{13}O_3N,\frac{1}{4}C_2H_4O$ requires C, 65·0; H, 5·85%).

(*b*) The temperature of a mixture of *m*-methoxybenzaldehyde (1·36 g.), aceturic acid (1·17 g.), acetic anhydride (4·1 c.c.), and triethylamine (1 c.c.) was raised from 30° to 65° during 5 days, then kept at 0° for 2 days, giving the crude azlactone, as above (0·5 g.; m. p. 98—101°).

Ethyl 6-Methoxy-1 : 2 : 3 : 4-tetrahydroisoquinoline-3-carboxylate (II; R = Et).—*m*-Methoxyphenylalanine was prepared by Chakravarti and Rao's method (*J.*, 1938, 172) except that it was purified through the copper salt. However, the intermediate *N*-benzoyl-β-*m*-methoxyphenylalanine (for which these authors quote m. p. 144°) after crystallisation first from methanol then from benzene formed colourless plates or prisms, m. p. 129° (Found: C, 68·2; H, 5·65. Calc. for $C_{17}H_{17}O_4N$: C, 68·65; H, 5·8%). The overall yield of *m*-methoxyphenylalanine from the azlactone was 30%.

Formalin (7 c.c.; 40 %) was added to a solution of *m*-methoxyphenylalanine (10 g.) in 0·5*N*-sodium hydroxide solution (100 c.c.). The solution was kept at room temperature for 4 hours, then heated in a water-bath at 37° for 15 hours, evaporated to half of its original volume (water-bath; reduced pressure),

acidified (Congo-red) by the addition of concentrated hydrochloric acid (about 7 c.c.) and then evaporated to complete dryness (water-bath; reduced pressure), the last traces of water being removed by the addition and distillation of a little absolute ethanol. The residue was treated with absolute ethanol (120 c.c.), and the cooled mixture saturated with dry hydrogen chloride and heated under reflux (water-bath) for 2½ hours. The bulk of the ethanol was removed by distillation (water-bath), the residue was dissolved in a small volume of cold water, and the solution was saturated with sodium carbonate and extracted with ether. The ether was removed from the dried (K_2CO_3) extract, and the residue distilled, the fraction, b. p. 155—165°/2 mm. (6·5 g.), being collected. The crude *picrate*, m. p. 183—186°, on being twice recrystallised from ethanol, formed pale yellow needles, m. p. 187—188° (Found: C, 49·45; H, 4·2. $C_{19}H_{17}O_9N,C_6H_3O_7N_3$ requires C, 49·15; H, 4·3%). The pure picrate was decomposed by treatment with cold 2*N*-sodium hydroxide solution, the base extracted with ether, the extract dried (K_2CO_3), the ether removed and the residue distilled, giving the *ester* as a pale yellow, viscous liquid, b. p. 160°/2 mm. (Found: C, 66·3; H, 7·25. $C_{12}H_{11}O_2N$ requires C, 66·4; H, 7·25%).

Methyl 6-Methoxy-1 : 2 : 3 : 4-tetrahydroisoquinoline-3-carboxylate.—This was prepared similarly and gave a *picrate* forming pale yellow needles from methanol, m. p. 185° (Found: C, 48·25; H, 4·1. $C_{12}H_{13}O_2N,C_6H_3O_7N_3$ requires C, 48·0; H, 4·0%).

6-Methoxy-1 : 2 : 3 : 4-tetrahydroisoquinoline-3-carboxylic Acid (II; R = H).—Sodium hydroxide (1·1 g.) in water (1·1 c.c.) was added to the ethyl ester (1·1 g.) in 95% ethanol (13 c.c.). The mixture was heated under reflux (water-bath) for 7 hours, the ethanol distilled off, the residue dissolved in water, and the solution neutralised with dilute acetic acid. The crude acid (0·47 g.) separated; recrystallised from water, it formed colourless leaflets, m. p. 302° (decomp.) (Found: C, 62·9; H, 6·35. Calc. for $C_{11}H_{13}O_3N$: C, 63·7; H, 6·3%). Chakravarti and Rao, *loc. cit.*, quote m. p. 263—264° (decomp.) for this acid.

Ethyl 6-Methoxyisoquinoline-3-carboxylate.—Ethyl 6-methoxy-1 : 2 : 3 : 4-tetrahydroisoquinoline-3-carboxylate (0·6 g.) was dehydrogenated with sulphur (0·24 g.) in tetralin (3 c.c.) as described for ethyl 1 : 2 : 3 : 4-tetrahydroisoquinoline-3-carboxylate. The product was not distilled, but was crystallised from benzene–light petroleum (yield: 0·23 g.; m. p. 98—102°); when recrystallised this afforded the *ester* as very pale-yellow prisms, m. p. 104—105° (Found: C, 67·95; H, 5·6. $C_{13}H_{13}O_3N$ requires C, 67·55; H, 5·6%). The *picrate* separated from ethanol as bright-yellow crystals, m. p. 181—182° (Found: C, 47·75; H, 3·7. $C_{19}H_{15}O_9N,C_6H_3O_7N_3,H_2O$ requires C, 47·7; H, 3·75%).

m-Methoxyphenylalanine Ethyl Ester.—*m*-Methoxyphenylalanine (0·5 g.) was heated under reflux with ethanolic hydrogen chloride for 1½ hours (water-bath), the bulk of the ethanol removed by distillation, the residue dissolved in cold water, the solution saturated with sodium carbonate and extracted with ether, the extract dried (K_2CO_3), the ether removed, and the residue distilled, yielding the ester (0·2 g.) as a liquid, b. p. 140°/2 mm. The *picrate* separated from ethanol as bright-yellow crystals, m. p. 159—160° (Found: C, 47·95; H, 4·6. $C_{12}H_{17}O_2N,C_6H_3O_7N_3$ requires C, 47·8; H, 4·45%).

Ethyl 6-Methoxy-2-3′-cyanopropyl-1 : 2 : 3 : 4-tetrahydroisoquinoline-3-carboxylate (III; R = CN).—A mixture of ethyl 6-methoxy-1 : 2 : 3 : 4-tetrahydroisoquinoline-3-carboxylate (5·2 g.), γ-bromobutyronitrile (4·1 g.), and anhydrous potassium carbonate (1·8 g.) was heated, with occasional stirring, for 6 hours in the water-bath. After cooling, water (50 c.c.) was added, the mixture extracted with ether, the extract dried (K_2CO_3), the ether removed, and the residue distilled (5·2 g.; b. p. 190—220°/2 mm.). On redistillation this yielded the *nitrile* as a pale-yellow, viscous liquid, b. p. 210°/2 mm. (Found: C, 67·2; H, 7·1. $C_{17}H_{20}O_3N_2$ requires C, 67·5; H, 7·25%).

Ethyl 6-Methoxy-2-3′-carbethoxypropyl-1 : 2 : 3 : 4-tetrahydroisoquinoline-3-carboxylate (III; R = CO_2Et).—The nitrile (III; R = CN) (5·2 g.) was converted into the diester as described for the preparation of ethyl 2-3′-carbethoxypropyl-1 : 2 : 3 : 4-tetrahydroisoquinoline-3-carboxylate in Part I (*loc. cit.*); the *ester* was obtained as a pale-yellow, viscous liquid (4·8 g.; b. p. 200°/2 mm.) (Found: C, 65·0; H, 7·9. $C_{19}H_{27}O_5N$ requires C, 65·3; H, 7·75%).

9-Keto-2′-methoxy-1 : 4 : 6 : 7 : 8 : 9-hexahydro-2 : 3-benzpyridocoline (IV).—The diester (III; R = CO_2Et) (4·8 g.) was subjected to the Dieckmann reaction as described in Part I for the preparation of 9-keto-1 : 4 : 6 : 7 : 8 : 9-hexahydro-2 : 3-benzpyridocoline, except that the subsequent hydrolysis was by heating of the mixture on the water-bath for 6 hours with hydrochloric acid (150 c.c.; 10%). The dried (K_2CO_3) ether extract obtained after evaporation and basification was concentrated to a very small volume, decanted from a little gummy material, and allowed to cool, whereupon the crude *ketone* (1·3 g.; m. p. 110—115°) crystallised. Recrystallisation, first from ether, then from benzene–light petroleum afforded orange-yellow plates (0·5 g.), m. p. 123—124° (Found: C, 72·1; H, 7·35. $C_{15}H_{17}O_3N$ requires C, 72·7; H, 7·40%). The *hydrochloride* separated from methanol–acetone as yellow tablets, m. p. 195—196° (Found: C, 62·1; H, 6·3. $C_{15}H_{18}O_3NCl$ requires C, 62·6; H, 6·7%). The *oxime* was prepared by heating under reflux a solution of the crude ketone (50 mg.), hydroxylamine hydrochloride (50 mg.), and fused sodium acetate (0·1 g.) in methanol (2 c.c.) for 2½ hours; the product (20 mg.) separated from methanol as almost colourless prisms, m. p. 223—224° (Found: C, 68·45; H, 7·25. $C_{15}H_{18}O_3N_2$ requires C, 68·3; H, 7·3%). The *phenylhydrazone* was prepared by heating a solution of the ketone (0·28 g.) in absolute ethanol with phenylhydrazine (0·14 g.) for 4 hours on the water-bath; from methanol (charcoal) it separated as very pale yellow prisms (0·33 g.), m. p. 85—90° after sintering at 75° (Found: C, 70·8; H, 7·65. $C_{26}H_{27}ON_3,CH_4O$ requires C, 71·4; H, 7·65%).

Catalytic Hydrogenation of the Ketone (IV).—The ketone (0·646 g.) in glacial acetic acid (10 c.c.) was hydrogenated at room temperature and atmospheric pressure, 1 mol. of hydrogen being absorbed during 30 minutes when Adams's catalyst (0·19 g.) was used. The filtered solution was evaporated to dryness (water-bath; reduced pressure), the residue dissolved in water and basified (Na_2CO_3), the solution extracted with chloroform, the extract dried (K_2CO_3), the chloroform distilled off, and the residue crystallised from methanol, giving a solid (0·225 g.; m. p. 161—165°); on concentration the mother-liquors afforded a further crop (0·13 g.; m. p. 155—164°). These two solids were combined ('crude A'). The methanol was distilled off from the mother-liquors, and the residue recrystallised from benzene–light petroleum, giving 'crude B' (0·13 g.; m. p. 122—132°). 'Crude A' was recrystallised first from methanol (giving 0·23 g.; m. p. 165—166°) and finally from benzene, yielding '*base* A' as colourless

crystals, m. p. 166° (Found: C, 72·2; H, 8·2. $C_{14}H_{19}O_3N$ requires C, 72·1; H, 8·15%). A mixture of '*base A*' (15 mg.) and acetic anhydride was warmed on the water-bath for 35 minutes, cooled, treated with water, and basified (NH_4OH), and the resulting white solid (13 mg.) washed with water, dried, and recrystallised from benzene–light petroleum, affording '*acetylated base* A' as colourless needles, m. p. 118° (Found: C, 69·75; H, 7·55. $C_{16}H_{21}O_4N$ requires C, 69·8; H, 7·65%). Solutions of '*base A*' (20 mg.) and of picric acid (30 mg.) in ethanol were mixed, the solution concentrated, and diluted with ether. The precipitate was recrystallised from a small volume of ethanol, gives '*base A picrate*' as yellow prisms (27 mg.), m. p. 144—145° after sintering at 141° (Found: C, 52·05; H, 5·2. $C_{14}H_{19}O_3N,C_6H_3O_7N_3$ requires C, 51·95; H, 4·8%). '*Crude B*' was recrystallised twice from benzene–light petroleum, giving '*base B*' as colourless prisms, m. p. 138—140° (Found: C, 71·9; H, 8·35. $C_{14}H_{19}O_3N$ requires C, 72·1; H, 8·15%). This (22 mg.) was acetylated as for '*base A*' and the product isolated by extraction with ether, removing the ether from the dried (K_2CO_3) extract and recrystallising the residue from light petroleum (b. p. 40—60°), giving '*acetylated base* B' as colourless crystals (9 mg.) m. p. 86—87° (Found: C, 69·4; H, 7·3; N, 5·1. $C_{16}H_{21}O_4N$ requires C, 69·8; H, 7·65; N, 5·1%).

Reduction of the Ketone (IV) *by the Pondorf–Meerwein Method.*—The ketone (0·23 g.) was treated with aluminium *iso*propoxide (0·2 g.) and *iso*propyl alcohol dropped in during the slow distillation (total volume, 7 c.c.). The solvent was finally removed on the water-bath under reduced pressure, the residue treated with water and sodium hydroxide solution and extracted with chloroform, the extract dried (K_2CO_3), and the solvent removed, leaving an oil which soon solidified. A benzene solution of the resulting solid was boiled with charcoal, filtered, concentrated, and diluted with light petroleum. The resulting solid was recrystallised first from methanol and finally from benzene–light petroleum, giving a product (40 mg.), m. p. 165—166° not depressed by admixture with '*base A*.' The methanol mother-liquors on evaporation gave a residue which when recrystallised twice from benzene–light petroleum afforded a product, m. p. 138—140° not depressed by admixture with '*base B*.'

2-*m*-*Methoxybenzyl*-2 : 3 : 4 : 5-*tetrahydro*-β-*carboline* (V).—Solutions of *m*-methoxyphenylpyruvic acid (2·6 g.) in water (60 c.c.) and of tryptamine hydrochloride (2·45 g.) in water (30 c.c.) were mixed and heated for 2 days on the water-bath. After being cooled, the resulting solid was collected, washed with water, and dried (3·55 g.). Recrystallised from 95% ethanol, this afforded the hydrochloride as colourless crystals (2·45 g.), m. p. 270° (decomp.). A portion was shaken with a mixture of dilute sodium hydroxide solution and ether until solution was complete, the ethanol layer was dried (K_2CO_3) and evaporated, and the residue was recrystallised from benzene–light petroleum, giving the *base* as colourless needles, m. p. 124° (Found: C, 78·6; H, 6·8. $C_{19}H_{20}ON_2$ requires C, 78·1; H, 6·85%).

3″-*Methoxy*-3 : 4 : 6 : 9-*tetrahydro*-7 : 8-*benzindolo*(2′ : 3′-1 : 2)*pyridocoline* (I; R = OMe).—(*a*) 9-Keto-2′-methoxy-1 : 4 : 6 : 7 : 8 : 9-hexahydro-2 : 3-benzpyridocoline phenylhydrazone (0·5 g.) was added to ice-cooled absolute ethanol (15 c.c.), previously saturated with hydrogen chloride. After 1 hour at 0°, the mixture was heated under reflux for 7 hours on the water-bath, the bulk of the ethanol removed by distillation, and the residue treated with water. The hydrochloride (0·3 g.) was collected, washed with water, and shaken vigorously with a mixture of dilute sodium hydroxide solution and ether until all was dissolved. The ethanol layer was dried (K_2CO_3), the ether removed, and the residue recrystallised from benzene–light petroleum (charcoal), affording the *base* as colourless plates (0·2 g.), m. p. 168° after sintering at 150° (Found, in material dried for 1 hour at 100°/1 mm.: C, 78·7; H, 6·6. $C_{20}H_{20}ON_2$ requires C, 78·95; H, 6·6%).

(*b*) 2-*m*-Methoxybenzyl-2 : 3 : 4 : 5-tetrahydro-β-carboline hydrochloride (2·45 g.) was dissolved in boiling water (1,100 c.c.), the solution cooled to 40° and treated with formalin (36·5 c.c.; 40%). The solution was kept at 40—45° for 3 days, basified (40% sodium hydroxide solution), and cooled, and the resulting white solid collected, washed with water, dried in a vacuum desiccator, and recrystallised first from a small volume of benzene (charcoal), then from benzene–light petroleum, giving the base (1·15 g.) as colourless plates, m. p. 169° after sintering at 150° (Found, in material dried for 1 hour at 100°/1 mm.: C, 79·2; H, 6·75. $C_{20}H_{20}ON_2$ requires C, 78·95; H, 6·6%). Mixed m. p., with product from (*a*), 169°.

5-*Methoxyhomophthalic Anhydride.*—5-Methoxyhomophthalic acid (Chakravarti and Swaminathan, *J. Indian Chem. Soc.*, 1934, **11**, 101) (1·4 g.) was heated under reflux for 2 hours with acetyl chloride (7 c.c.), the mixture evaporated to dryness (water bath; reduced pressure), and the residue recrystallised from benzene (charcoal), giving the *anhydride* (1·1 g.) as creamy white plates, m. p. 171° (Found: C, 62·6; H, 3·85. $C_{10}H_8O_4$ requires C, 62·5; H, 4·15%).

N-2′-3″-*Indolylethyl*-2-*carboxy*-5-*methoxyphenylacetamide* (VI).—A solution of tryptamine (1·06 g.) in pure dry chloroform (25 c.c.) was added to one of the above anhydride (1·25 g.) in chloroform (45 c.c.). The mixture was heated under reflux for 8 hours, concentrated to 25 c.c., and allowed to cool. The *acid* was collected, washed with chloroform, and dried (2 g.; m. p. 169—170°); recrystallised from methanol, this afforded colourless crystals, m. p. 170—171° (Found: C, 67·6; H, 6·0. $C_{20}H_{22}O_4N_2$ requires C, 68·2; H, 5·7%).

Attempted Synthesis of the Hexahydro-Derivative of (IV).—Ethyl 6-methoxy-1 : 2 : 3 : 4-tetrahydroisoquinoline-3-carboxylate (4·76 g.) in ethanol (100 c.c.) was hydrogenated for 7 hours at 155—160° in the presence of freshly reduced nickel–kieselguhr catalyst (0·95 g.), the initial hydrogen pressure being 80 atmospheres at room temperature. The ethanol was removed from the filtered solution, and the residue distilled at 2 mm. pressure giving (*a*) a liquid (0·45 g.), b. p. 137—150°; (*b*) a liquid (3·8 g.), b. p. 150—157° (mainly 155°) (Found: C, 67·7; H, 8·7. $C_{13}H_{23}O_3N$ requires C, 64·75; H, 9·55%). When treated with γ-bromobutyronitrile as described for the preparation of (III; R = CN), (*b*) yielded a gum (1·72 g.), b. p. 140°/2 mm. On treatment with ethanolic hydrogen chloride, this gave another gum, which was subjected to the Dieckmann reaction, giving, after distillation, a red gum (0·27 g.) (Found: C, 71·0; H, 8·8. $C_{14}H_{23}O_3N$ requires C, 70·9; H, 9·7%). Attempts to prepare a crystalline oxime or semicarbazone from this failed; and no crystalline picrate could be obtained from this or from the intermediate products.

When the hydrogenation was carried out at higher temperatures, the reduced ester had a lower b. p., and the analysis (C, 70; H, 10%) indicated that extensive hydrogenation and/or hydrogenolysis had occurred. Hydrogenation at atmospheric pressure of the ester (1 g.) in acetic acid in the presence of

Adams's catalyst (0·1 g.) gave a product (0·5 g.) apparently similar to the above (Found: C, 66·7; H, 9·8%).

Reduction of 3"-Methoxy-3 : 4 : 6 : 9-tetrahydro-7 : 8-benzindolo(2' : 3'-1 : 2)pyridocoline.—The base (1·2 g.) was dissolved in liquid ammonia (ca. 300 c.c.) contained in an un-silvered Dewar vessel. Sodium (2·3 g.) and *tert.*-butanol (5 c.c.) were added with occasional stirring alternately each in 6 equal portions during 1 hour. After a further 1 hour, more sodium (0·6 g.) was added; an hour later, methanol was added dropwise until the solution was colourless. The solution was then poured into a beaker, the ammonia allowed to evaporate, and the residue treated with ice and water. The resulting solid was collected, washed with water, and dried in a vacuum desiccator; it (1·05 g.) had m. p. 179—183°. Recrystallised from benzene, this gave '*base* C' as shining, colourless leaflets (0·95 g.), m. p. 183—184° (Found, in material dried at 100°/1 mm. for ½ hour: C, 78·6; H, 7·3. $C_{20}H_{22}ON_2$ requires C, 78·45; H, 7·2%).

A solution of this (0·95 g.) in methanol (55 c.c.) was treated with 2N-hydrochloric acid (19 c.c.), heated on the water-bath for 1½ hours, and diluted with hot water (25 c.c.). The bulk of the methanol was removed by distillation from the water-bath, and the residue was basified (2N-sodium hydroxide solution) and cooled; the resulting solid was washed with water and dried in a vacuum desiccator (0·88 g.). Recrystallised four times from methanol this gave '*base* D,' as long, yellow needles, m. p. 260—261° (decomp.) (Found: C, 77·8; H, 6·95. $C_{19}H_{20}ON_2$ requires C, 78·05; H, 6·85%). Light absorption in ethanol: $\lambda_{max.}$ 2710 A.; log ε 3·97.

The mother-liquors from the first recrystallisation of '**base** *D*' on concentration gave a small amount of '*base* E' which, after recrystallisation from methanol, formed yellow plates, m. p. 211—212° (Found: C, 77·85; H, 6·85. $C_{19}H_{20}ON_2$ requires C, 78·05; H, 6·85%).

(±)-*Yohimbone.*—'**Base** *D*' (0·469 g.) in glacial acetic acid (15 c.c.) was hydrogenated at room temperature and pressure in the presence of previously reduced Adams's catalyst (70 mg.), and the hydrogenation was interrupted after the uptake of 1 mole of hydrogen in 38 minutes. The solvent was removed from the filtered solution, the residue dissolved in warm water, cooled, and basified (N-sodium hydroxide solution), and the precipitate collected, washed with water, dried, and crystallised from methanol (charcoal) giving the base (0·35 g.; m. p. 242—244°). After being twice recrystallised from methanol the (±)-*yohimbone* formed long, slender, colourless needles, m. p. 266° (decomp.) after darkening and sintering at 265° (Found: C, 77·6; H, 7·9. $C_{19}H_{22}ON_2$ requires C, 77·55; H, 7·5%). Light absorption in ethanol: $\lambda_{max.}$ 2780 A.; log ε 3·91. The *dinitrophenylhydrazone hydrochloride* separated from methanol as orange-red crystals which became black at ca. 280°, but did not melt below 320° (Found: C, 57·8; H, 5·4. $C_{31}H_{34}O_9N_6,HCl,\frac{1}{2}H_2O$ requires C, 57·75; H, 5·4%).

Resolution of (±)-*Yohimbone.*—Fractional crystallisation of the (+)-tartrate gave little resolution. The (+)-camphor-10-sulphonate of (±)-yohimbone (0·53 g.) was recrystallised six times from ethanol and a base (25 mg.), m. p. 299—301° (decomp.), $[\alpha]_D^{20}$ +93°, recovered. The final resolution was therefore carried out as follows: A solution of (±)-yohimbone (0·77 g.) in hot ethanol was treated with one of (−)-camphor-10-sulphonic acid (0·74 g.), and the mixture concentrated to a small volume and kept overnight in a refrigerator. The resulting solid (0·6 g.) was recrystallised nine times from ethanol, giving the (−)-base-(−)-camphorsulphate (0·16 g.) as colourless crystals, m. p. 294—296° (decomp.). A solution of this in hot water (40 c.c.) was cooled and basified (N-sodium hydroxide solution), the precipitate taken up in chloroform, the solution dried (K_2CO_3), the solvent removed, and the residue recrystallised from methanol, giving (−)-yohimbone (70 mg.) as long, slender, colourless needles; m. p. 305—306° (decomp.) after darkening at 285°, not depressed by admixture with natural yohimbone of m. p. 304—305° (decomp.) (Found: C, 77·8; H, 7·9. $C_{19}H_{22}ON_2$ requires C, 77·55; H, 7·5%). It had $[\alpha]_D^{20}$ −1·371° (in pyridine, *c*, 2·585, *l*, 0·5, *d* 0·9922), $[\alpha]_D^{20}$ −106° (Witkop, *loc. cit.*, gives −103·9° and −105·8° for *c*, 0·8565 and 0·652, respectively). The picrate of the synthetic (−)-base, prepared as described by Witkop for that of yohimbone, had m. p. 169° (Witkop gives 171°). For yohimbone methiodide Witkop gives m. p. 290° (decomp.) and m. p. 286° (decomp.); when prepared as he describes, however, it was found to have m. p. 296—297° (decomp.). The methiodide of the synthetic (−)-base had m. p. 297—298°, not changed by recrystallisation from methanol–acetone, and not depressed by admixture with the above.

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319. *The Constitution of Yohimbine and Related Alkaloids. Part V. Some Attempts to synthesise Sempervirine.*

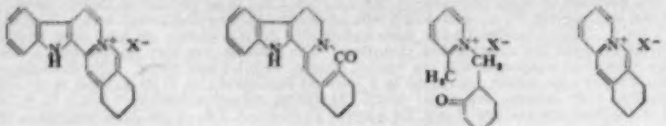
By G. A. SWAN.

A number of experiments relating to unsuccessful attempts to synthesise sempervirine are recorded.

THE synthesis of 3 : 4-dihydro-7 : 8-benzindolo(2' : 3'-1 : 2)pyridocoline, not identical with sempervirine, was described in Part III (*J.*, 1949, 1720).

Experiments were then initiated towards the synthesis of (I), which appeared to be the most

likely structure for the salts of sempervirine. A short time later, Dr. T. S. Stevens kindly sent the author a copy, before publication, of a communication (Bentley and Stevens, *Nature*, 1949, 164, 141) in which structure (I) was suggested and supported by experimental evidence. Later, the communications of Woodward and Witkop (*J. Amer. Chem. Soc.*, 1949, **71**, 379), putting forward the same structure and of Woodward and McLamore (*ibid.*, p. 379) describing the synthesis of sempervirine methosalts, came to hand. The synthesis of (I) by a number of possible routes has been investigated; but all proved unpromising and were abandoned, although the positive results obtained are recorded in this paper.



(I.) (II.) (III.) (IV.)

Kon and Nanji (*J.*, 1932, 2426) found that 3 : 4 : 5 : 6-tetrahydrohomophthalic acid (2-carboxy-1-*cyclo*hexenylacetic acid) was unaffected by acetyl chloride even in a sealed tube; but that with acetic anhydride it gave an impure, coloured liquid, believed to consist mainly of the hydroxy-anhydride. Repetition of this work showed that the action of acetyl chloride for 30 minutes on the water-bath gave (in good yield) a pale yellow liquid which appeared to be the anhydride; whilst the action of acetic anhydride gave a small amount of this, together with a neutral compound, $C_{14}H_{20}O_5$, crystallising in colourless needles, m. p. 147—148°, which has not been further investigated. The anhydride was treated with tryptamine, and the acidic product treated first with diazomethane, then with phosphoryl chloride, in the hope of obtaining (II); but the only product isolated formed bright yellow needles, m. p. 262°, and contained chlorine. The neutral *N*-(3′-indolyl-2-ethyl)-3 : 4 : 5 : 6-tetrahydrohomophthalimide simultaneously produced in the reaction between the anhydride and tryptamine also failed to give (II) on treatment with phosphoryl chloride.

In model experiments, attempts were made to prepare (III; X = I) in the hope that it would undergo cyclisation and dehydrogenation to give (IV). 2-Hydroxymethyl*cyclo*hexanone was prepared essentially by Décombe's method (*Compt. rend.*, 1941, **213**, 579); but its b. p. was found to differ widely from that recorded. Attempts to convert this alcohol into the corresponding bromide and to quaternise this with 2-picoline to give (III) were not promising, nor was a similar approach by the action of paraformaldehyde and hydrochloric acid on *cyclo*hexanone (cf. Sorkin and Hinden, *Helv. Chim. Acta*, 1949, **32**, 63).

By the action of phosphoryl chloride, 3-2′-(chloroacetamido)ethylindole was cyclised to 2-chloromethyl-4 : 5-dihydro-β-carboline hydrochloride, which reacted with potassium cyanide to give 2-cyanomethyl-4 : 5-dihydro-β-carboline; but attempts to dehydrogenate this to 2-cyanomethyl-β-carboline were unsuccessful. The condensation of ethyl cyanoacetate with tryptamine gave 3-2′-(cyanoacetamido)ethylindole; but the cyclisation of this by phosphoryl chloride gave only a very low yield of 2-cyanomethyl-4 : 5-dihydro-β-carboline.

The preparation of 2-keto-1-nitromethyl*cyclo*hexanol is described in the experimental section.

In Part III it was suggested, on the evidence of ultra-violet absorption spectra, that the action of light on a solution of 3 : 4-dihydro-7 : 8-benzindolo(2′ : 3′-1 : 2)pyridocoline involves

(V.) (VI.)

conversion into a product of the type (V). Edwards and Marion (*J. Amer. Chem. Soc.*, 1949, **71**, 1694) have also described the synthesis of the base [the m. p. of their compound is different from that recorded in Part III, but it depends on the rate of heating], and have isolated the irradiation product, the hydrochloride of which they formulate as (VI; X = Cl), the analytical results being in agreement with the formula $C_{19}H_{14}ON_2Cl,H_2O$. However, we find that when the irradiation product is dried at 100°/1 mm., it analyses as $C_{19}H_{14}N_2Cl$ and appears to be

identical with 3 : 4-dihydro-7 : 8-benzindolo[2' : 3'-1 : 2]pyridicolinium chloride (V; X = Cl), *e.g.*, the behaviour on catalytic hydrogenation is exactly that described for (V; X = Cl) in Part III.

Experimental.

(All m. p.s are uncorrected.)

The Action of Acetic Anhydride on 2-Carboxy-1-cyclohexenylacetic Acid.—The acid (Kon and Nanji, *loc. cit.*; Grewe and Mondon, *Chem. Ber.*, 1948, **81**, 279) (0·63 g.) was heated under reflux for 3 hours with acetic anhydride (2 c.c.), and the product distilled at ca. 1 mm., giving (*a*) a moderately viscous yellow oil (0·18 g.; b. p. 150—160°) and (*b*) an extremely viscous yellow gum (0·25 g.; b. p. about 160°). The gum was dissolved in benzene, and the solution diluted with light petroleum. The precipitated solid was recrystallised from benzene–light petroleum (charcoal), giving a *compound* as colourless needles, m. p. 147—148° [Found: C, 80·0, 80·75, 80·55; H, 7·55, 7·95, 7·45%; *M* (Rast), 306. $C_{18}H_{20}O_3$ requires C, 80·6; H, 7·45%; *M*, 268].

The Action of Acetyl Chloride on 2-Carboxy-1-cyclohexenylacetic Acid.—The acid (2·4 g.) was heated under reflux for 30 minutes with acetyl chloride (10 c.c.) and the product distilled, giving the *anhydride* (1·7 g.) as a moderately viscous, pale yellow oil, b. p. 180—182°/1 mm. (Found: C, 65·4; H, 6·5. $C_9H_{10}O_3$ requires C, 65·1; H, 6·0%). This was reconverted into the original acid by being boiled with N-sodium hydroxide solution.

Attempted Condensation of the Anhydrides with Tryptamine and Cyclisation of the Product.—A solution of tryptamine (1·46 g.) in pure, dry chloroform (20 c.c.) was added to one of the anhydride (1·62 g.) in chloroform (10 c.c.), and the mixture heated under reflux for 7 hours on the water-bath. The solution was cooled in ice, and extracted three times with 2N-sodium hydroxide solution; the combined alkaline layer was extracted with ether, and then acidified (concentrated hydrochloric acid) with ice-cooling. The precipitated gum was dissolved in chloroform, the extract dried (Na_2SO_4), the solvent removed, the residue dissolved in methanol, and the solution cooled in ice and treated with excess of an ethereal solution of diazomethane. After 2 hours, the solution was evaporated to dryness and the residue kept overnight in a vacuum desiccator, giving a greenish, sticky mass (1·6 g.). This was heated for 35 minutes under reflux in a current of nitrogen with phosphoryl chloride (21 c.c.), the solution evaporated to dryness (water-bath; reduced pressure), and the residue cooled and stirred with water, dilute sodium hydroxide solution being gradually added until the solution was alkaline. The resulting solid was collected, washed with water, dried in a vacuum desiccator, and extracted with chloroform in a Soxhlet apparatus. During the first few minutes of the extraction, a good deal of dark brown material was extracted; this was rejected and the extraction continued. After several hours, the extract was cooled and filtered, and the resulting yellow solid (0·15 g.) washed with chloroform and recrystallised from methanol (charcoal), giving bright yellow needles, which were dried for ½ hour at 100°/1 mm. and then had m. p. 262° (Found: C, 61·65; H, 6·0; N, 7·95%).

From the neutral material produced in the tryptamine condensation *N-(3'-indolyl-2-ethyl)-3 : 4 : 5 : 6-tetrahydrokomophthalimide* could be isolated. This could also be prepared by heating under reflux for 13 hours a solution in dry benzene (17 c.c.) of tryptamine (0·45 g.) and the anhydride (0·55 g.). After cooling, the sticky solid was collected, washed with benzene, and crystallised from chloroform, methanol, or acetone, giving the imide (0·25 g.) as colourless needles, m. p. 230—231° (Found: C, 74·2; H, 6·7; N, 9·6. $C_{19}H_{20}O_2N_2$ requires C, 74·0; H, 6·5; N, 9·1%).

2-Hydroxymethylcyclohexanone.—A mixture of *cyclo*hexanone (50 c.c.), water (100 c.c.), and potassium carbonate (1 g.) was stirred vigorously at 30—35°, while formalin (75 c.c.; 40%) was added during 1 hour, after which stirring was continued for a further 1 hour. The cooled mixture was extracted with ether, and the extract dried (K_2CO_3) and distilled, giving (*a*) *cyclo*hexanone (27 c.c.); (*b*) a mobile, colourless liquid, b. p. 112—126°/12 mm. (8 g.); and (*c*) a viscous, colourless liquid, b. p. 126—175°/12 mm. (6 g.). Redistilled, the *ketone* (*b*) (6·8 g.) had b. p. 110°/11 mm. (Found: C, 65·8; H, 9·55. $C_7H_{12}O_2$ requires C, 65·6; H, 9·4%). [The phenylhydrazone formed pale yellow prisms, m. p. 127—128°, from methanol.]

2-Chloromethyl-4 : 5-dihydro-β-carboline Hydrochloride.—A mixture of 3-2'-(chloroacetamido)ethylindole (von Braun, Bahn, and Münch, *Ber.*, 1929, **62**, 2760) (0·53 g.), toluene (2·5 c.c.), and phosphoryl chloride (0·75 c.c.) was heated under reflux in a current of nitrogen for 1 hour, cooled, and treated with light petroleum (b. p. 40—60°). The solvents were decanted from the residual gum, which was then treated with warm water. The cooled, aqueous solution was extracted with ether, filtered, basified (ammonia solution), and extracted with ether. The latter ether extract was filtered and stirred with a slight excess of concentrated hydrochloric acid. The ether was decanted from the precipitated yellow solid, which was stirred with acetone, and the product was collected and washed with acetone; it (0·24 g.) then had m. p. 225° (decomp.). Recrystallised from aqueous acetone the *hydrochloride* was obtained as shining, dark, brownish-red prisms, m. p. 230° (decomp.) (Found: C, 56·4; H, 5·5. $C_{12}H_{13}N_2Cl_3$ requires C, 56·45; H, 4·7%).

2-Cyanomethyl-4 : 5-dihydro-β-carboline.—A solution of the hydrochloride (0·15 g.) in water (1·5 c.c.) was treated with one of potassium cyanide (0·15 g.) in water (0·7 c.c.). After being cooled and stirred, the precipitated gum rapidly solidified and was collected, washed with water, and heated under reflux on the water-bath for 15 minutes with a solution of potassium cyanide (0·25 g.) in water (0·7 c.c.) and ethanol (1 c.c.). Part of the ethanol was removed by distillation, the solution was cooled and the resulting brown solid separated from the black tar. The former was recrystallised from aqueous methanol (the first part to separate being rejected) giving the *base* as a yellowish buff powder (70 mg.), m. p. 202—203° (Found: C, 74·5; H, 5·55. $C_{13}H_{11}N_3$ requires C, 74·65; H, 5·3%).

3-2'-(Cyanoacetamido)ethylindole.—A mixture of ethyl cyanoacetate (0·33 g.) and tryptamine (0·45 g.) was heated for 2 hours on the water-bath. The product was stirred with dilute hydrochloric acid and cooled, whereupon it solidified; the resulting solid was collected, washed with water, and recrystallised from aqueous methanol (charcoal), giving the *amide* as almost colourless plates (0·49 g.), m. p. 92—93° (Found: C, 68·6; H, 5·9. $C_{13}H_{13}ON_3$ requires C, 68·7; H, 5·75%).

2-*Keto*-1-*nitromethylcyclohexanol*.—A mixture of nitromethane (2·7 c.c.) and *cyclo*hexane-1 : 2-dione (Bitz, Davis, and Gadds, *J. Org. Chem.*, 1947, **12**, 122) (6 g.) was cooled in ice and treated with piperidine (0·3 c.c.). After 3 days at room temperature, the mixture was dissolved in chloroform, and the solution washed with dilute hydrochloric acid and sodium hydrogen carbonate solution, and dried (Na_2SO_4). The solvent was removed and the residue treated with light petroleum (b. p. 40—60°) whereupon it crystallised. The solid was collected and washed with light petroleum, and the crude *product* (2 g.; m. p. 88—89°) recrystallised from benzene, giving colourless plates, m. p. 90—91°, b. p. 135—140°/1 mm. (Found : C, 49·0; H, 6·4. $C_7H_{11}O_4N$ requires C, 48·6; H, 6·4%).

The Oxidation Product of **2 : 4-*Dihydro*-7 : 8-*benzindolo* (2′ : 3′-1 : 2)*pyridocolline Hydrochloride*.**—This was prepared according to Edwards and Marion's method, and dried for 3½ hours at 100°/1 mm. (Found : C, 74·3; H, 5·4. Calc. for $C_{13}H_{14}N_2Cl$: C, 74·4; H, 4·9%).

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320. *Cyclic Meso-ionic Compounds. Part III. Further Properties of the Sydnones and the Mechanism of their Formation.*

By WILSON BAKER, W. D. OLLIS, and V. D. POOLE.

Some substituted *NC*-diarylsydnones have been prepared for dipole-moment investigation, and the direct nitration of *N*-phenylsydnone in the heterocyclic nucleus has been achieved.

When heated with benzylamine the sydnones are smoothly converted into the benzylamides of *N*-substituted *N*-nitrosoglycines (IV); reaction does not occur with aniline.

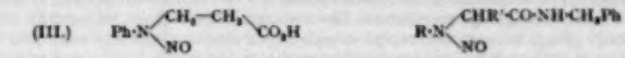
The usual method of preparation of a sydnone, *e.g.*, *N*-phenylsydnone, by heating *N*-nitroso-*N*-phenylglycine (I; R = Ph, R′ = H) with acetic anhydride has been shown to proceed *via* the mixed anhydride (VIII) of acetic acid and *N*-nitroso-*N*-phenylglycine. This anhydride (VIII) has been prepared from acetyl chloride and the potassium salt of *N*-nitroso-*N*-phenylglycine; it passes slowly into *N*-phenylsydnone with loss of acetic acid when kept at room temperature, but rapidly when heated. The acid chloride of *N*-nitroso-*N*-phenylglycine is even more reactive and cannot be isolated, since it passes immediately into *N*-phenylsydnone with loss of hydrogen chloride. The mechanisms of these reactions and their significance in connection with the formation of oxazolones from α-acylamido-acids is discussed. Reaction of trifluoroacetic anhydride with *N*-nitroso-*N*-phenylglycine results in the immediate formation of *N*-phenylsydnone in 93% yield.

Suggestions governing the use of the term meso-ionic are made, and a note on the resonance energy of meso-ionic compounds is given. Unsuccessful attempts have been made to prepare meso-ionic compounds of the type (XXIV).

THE properties of the sydnones, prepared by dehydration of *N*-nitroso-*N*-aryl(or -alkyl)-glycines (I), were interpreted in Part I of this series (Baker, Ollis, and Poole, *J.*, 1949, 307) on the basis of a five-membered cyclic structure (II) which could not be represented, even approximately, by any conventional covalent formula. It was shown that the sydnones must be regarded as possessing a single hybrid structure of aromatic type, derived from a number of contributing forms all of dipolar (zwitterionic) or polypolar nature. Such compounds were termed meso-ionic, and the symbol ± was used, as in (II), to indicate this hybrid character. This view of the structure of the sydnones was strongly supported in Part II (Hill and Sutton, *J.*, 1949, 746) by a study of their dipole moments.

Several new *NC*-diarylsydnones have been prepared for further dipole-moment investigation. α-Halogeno-phenylacetyl chlorides, prepared either by the action of phosphorus pentachloride on a mandelic acid or by bromination of a phenylacetyl chloride, were converted *via* the methyl α-halogeno-phenylacetates into the methyl α-arylamino-phenylacetates by reaction with aniline, *p*-toluidine, or *p*-chloroaniline, and then hydrolysed to the α-arylamino-phenylacetic acids. Nitrosation then yielded the *N*-nitroso-*N*-arylamino-phenylacetic acids (I; R and R′ = aryl groups), which were then dehydrated with acetic anhydride to the *NC*-diarylsydnones (II; R and R′ = aryl groups). The following sydnones were prepared in this way : *N*-phenyl-*C*-*p*-chlorophenylsydnone (II; R = Ph, R′ = *p*-C_6H_4Cl); *NC*-di-*p*-chlorophenylsydnone (II; R = R′ = *p*-C_6H_4Cl); *N*-phenyl-*C*-*p*-tolylsydnone (II; R = Ph, R′ = *p*-C_6H_4Me); *NC*-di-*p*-tolylsydnone (II; R = R′ = *p*-C_6H_4Me). These *NC*-diarylsydnones fluoresce in ultra-violet light, which indicates a certain degree of conjugation throughout the whole molecule.

Of interest to the general question of the structure of the sydnones is the observation that *N*-nitroso-β-anilinopropionic acid (III) is not dehydrated by acetic anhydride. If the

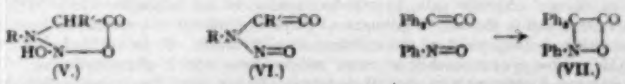


sydnones were correctly represented by the bicyclic structure originally proposed (Earl and Mackney, *J.*, 1935, 899; Earl and Eade, *J.*, 1946, 591), then *N*-nitroso-β-anilinopropionic acid (III) should, when dehydrated, give a bicyclic structure containing a bridged 6-membered heterocyclic ring. On the basis of a meso-ionic structure for the sydnones, (III) is incapable of dehydration to such a compound, as the presence of the methylene group in the 6-membered ring would prevent the possession of a similar cyclic, electronic system.

The direct chlorination of *N*-phenylsydnone in acetic acid to give *C*-chloro-*N*-phenylsydnone has been described by Eade and Earl, but we find that the reaction proceeds more smoothly in acetic anhydride at 0°. *N*-*p*-Chlorophenylsydnone is similarly halogenated to *C*-chloro-*N*-*p*-chlorophenylsydnone. It has also been found possible to nitrate *N*-phenylsydnone in concentrated sulphuric acid at −10° to give *C*-nitro-*N*-phenylsydnone, but attempts to reduce this to the amine have not succeeded. The position of the nitro-group follows from the fact that the substance differs from the known *N*-*o*-, *N*-*m*-, and *N*-*p*-nitrophenylsydnones (Eade and Earl, *loc. cit.*). *C*-Bromo-*N*-phenylsydnone could not be made to yield a Grignard reagent, and it was unaffected by refluxing with sodium in benzene or dioxan. The persistent non-reactivity of the benzene nucleus in *N*-arylsydnones is further proof of the fact, already discussed in Part I, that the nitrogen atom to which it is attached bears a large fractional positive charge and is certainly not tervalent and neutral.

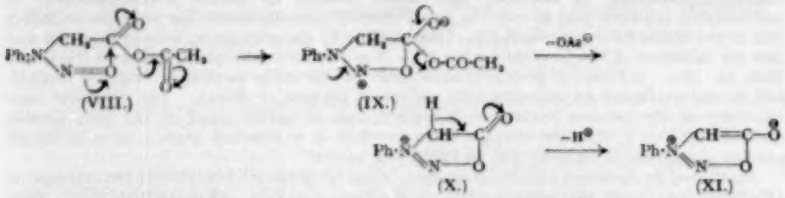
Reaction of the Sydnones with Benzylamine.—When sydnones are heated with benzylamine at 120—130° they yield the benzylamides of *N*-nitroso-*N*-aryl(or -alkyl)glycines (IV). Thus *N*-phenylsydnone, *N*-benzylsydnone, *N*-*cyclo*hexylsydnone, and *NC*-diphenylsydnone yield the benzylamides (IV; R′ = H, R = Ph, CH_2Ph, and *cyclo*hexyl, respectively). The benzylamide (IV; R′ = H, R = Ph) of *N*-nitroso-*N*-phenylglycine was also prepared by the nitrosation of the benzylamide of *N*-phenylglycine. This reaction of sydnones with benzylamine does not occur when the reactants are refluxed in benzene solution, and no reaction occurs when a sydnone is heated with aniline at 125°. The "lactone" group in the sydnone molecule is therefore much less reactive than a normal lactone, and this is consistent with the meso-ionic structure which does not permit the normal cationoid properties to be exhibited by the lactonic carbonyl group (see the contributors to the hybrid structure set out in Part I).

Mechanism of Sydnone Formation.—No satisfactory explanation has yet been given of the mechanism of the formation of sydnones from *N*-nitroso-*N*-aryl- or -alkyl-glycines (I). By analogy with the formally related γ-keto-acids, the reaction might proceed *via* a hydroxylactone-like intermediate (V) (cf. Earl and Mackney, *J.*, 1935, 899). The γ-keto-acids are, however, converted by acetic anhydride into the γ-acetoxy-lactones, and (V), if formed, might therefore be expected to yield its *O*-acetyl derivative rather than to undergo dehydration to a sydnone. A second possibility discussed by Earl (*Nature*, 1946, **158**, 909) is that the nitroso-acid (I) might undergo dehydration to a nitroso-keten (VI) with subsequent addition of the nitroso-oxygen atom to the carbonyl-carbon atom, by analogy with one mode of addition of a nitroso-compound to a keten to give a 4-membered lactone as, for example, in the case of the formation of the compound (VII) (Staudinger and Jelagin, *Ber.*, 1911, **44**, 365). There is, however, no evidence of the formation of ketens by the dehydration of carboxylic acids with acetic anhydride, and the fact that the sydnones may be prepared from the *N*-nitrosoglycines (I) by reaction with acetic anhydride in the cold makes it extremely unlikely that the keten (VI) is an intermediate.



Some light was thrown on the mechanism of sydnone formation by the observation that *N*-phenylsydnone may be prepared by the action of acetic anhydride on the potassium salt of *N*-nitroso-*N*-phenylglycine. Owing to the insolubility of the potassium salt the reaction proceeds more slowly than with the free acid, but dissolution and sydnone formation take place rapidly if one equivalent of acetyl chloride is added. The reaction of the potassium salt

with acetyl chloride could scarcely proceed otherwise than by formation of the mixed anhydride (VIII) of *N*-nitroso-*N*-phenylglycine and acetic acid, and this will almost certainly be formed also by the action of acetic anhydride on the free nitroso-acid. In (VIII), as in other anhydrides, one or other of the carbonyl groups may behave like a normal ketonic group rather than like a carboxylic-carbonyl group, because the bridge oxygen atom cannot effectively neutralise the cationoid character of both carbonyl groups simultaneously (cf. the reactivity of a methyl group in acetic anhydride in the Perkin reaction, the carbonyl reactivity in phthalic anhydride, etc.). The glycine carbonyl group may, therefore, in the mixed anhydride (VIII) develop much stronger cationoid properties than in the free acid (or in the salt) so that attack by the anionoid nitroso-oxygen atom becomes possible (see VIII). These changes lead to (IX) which by a natural process loses an acetate anion, and probably undergoes shift of the positive charge to give the cation (X). This, in turn, by the normal electronic movements shown, passes by loss of a proton (a process analogous to enolisation) into one of the more important contributors (XI) (see dipole moment evidence in Part II; Hill and Sutton, *J.*, **1949**, 746) to the hybrid sydnone structure. The overall change involves loss of acetic acid from (VIII), and the final distribution



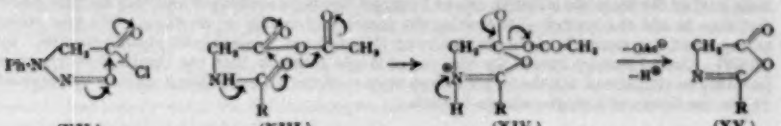
of the electrons to give the single hybrid sydnone molecule will follow the formation of (XI) or of any structure containing the same heterocyclic ring. The alternative cyclisation involving the other carbonyl group is much less likely as it would lead to the formation of a seven-membered ring, and this could not in any case yield a sydnone by loss of acetic acid.

Evidence that the usual method of sydnone formation proceeds as just described is provided by the properties of the mixed anhydride (VIII). This substance was obtained by treating a suspension of the potassium salt of *N*-nitroso-*N*-phenylglycine in benzene with rather less than one equivalent of acetyl chloride, and was isolated from the filtrate as a low-melting unstable solid. At room temperature the anhydride (VIII) loses acetic acid and passes into the much higher-melting sydnone during the course of five days; the change also occurs, giving very high yields, in hot benzene, and is almost quantitative when the solid is kept under diminished pressure over potassium hydroxide at room temperature. The anhydride (VIII) clearly behaves as a true intermediate.

These experiments and considerations suggested a new method by which sydnones might be prepared. The very great chemical activity exhibited by the acid chlorides may be ascribed to the abnormally high degree of cationoid character possessed by the carbon atom, which may exceed even that in an aldehyde or ketone owing to the strong inductive effect of the chlorine atom, $O{=}C{\rightarrow}Cl$. Hence the acid chloride (XII) of *N*-nitroso-*N*-phenylglycine should undergo even more ready transformation into *N*-phenylsydnone than the mixed anhydride (VIII); the same series of changes as (VIII) to (XI) would occur, but in this case the reaction would proceed with loss of hydrogen chloride. There is, however, one complicating factor, namely, that *N*-phenylsydnone readily reacts with hydrogen chloride in a variety of solvents to give coloured decomposition products. Nevertheless, reaction of *N*-nitroso-*N*-phenylglycine in cold ethereal solution with thionyl chloride gave extremely rapidly, if not immediately, a 28% yield of *N*-phenylsydnone, and in dioxan, in presence of three equivalents of pyridine to react with the hydrogen chloride, a 75% yield of the sydnone was obtained. It seems likely that the acid chloride (XII) passes spontaneously at room temperature into *N*-phenylsydnone. This new method of sydnone formation possesses advantages over the usual much slower dehydration of the *N*-nitroso-*N*-arylglycines with acetic anhydride.

A very close parallel may be drawn between the formation of sydnones and the preparation of 2-substituted oxazol-5-ones (XV) by the action of acetic anhydride on α-acylamido-acids. The latter must now be regarded as occurring *via* the mixed anhydride (XIII), in which the electronic changes shown in (XIII) and (XIV) lead to the loss of acetic acid and the formation

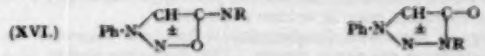
of the oxazolone (XV). The parallel extends also to the spontaneous conversion of the chloride of *N*-nitroso-*N*-phenylglycine (XII) into *N*-phenylsydnone, since it was found by Barber, Gregory, Slack, Stickings, and Woolman (*CPS* **234**; "The Chemistry of Penicillin," Princeton Univ. Press, 1949, p. 731, 746) that the acid chlorides of the α-acylamido-acids pass directly into the oxazolone hydrochlorides; the mechanism is doubtless similar to that given above.



(XII.) (XIII.) (XIV.) (XV.)

One further novel method for the preparation of sydnones from *N*-nitroso-*N*-arylglycines has resulted from the foregoing experiments. It has been found by Bourne, Stacey, Tatlow, and Tedder (*J.*, 1949, 2976) that trifluoroacetic anhydride rapidly brings about the complete formation of esters from alcohols or phenols and acids at room temperature, and it was suggested that the reaction proceeded *via* the mixed anhydride of the carboxylic acid and trifluoroacetic acid, $R{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CF_3$. If this is indeed the case, then trifluoroacetic anhydride should react with *N*-nitroso-*N*-arylglycines to give, for example, the mixed anhydride $Ph{\cdot}N(NO){\cdot}CH_2{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CF_3$, which, in view of the very powerful electrophilic properties of the CF_3 group, should lose trifluoroacetic acid and pass into *N*-phenylsydnone even more easily than the related acetyl derivative (VIII). This expectation was fully realised as it was found that addition of trifluoroacetic anhydride to an ethereal solution of *N*-nitroso-*N*-phenylglycine at $-5°$ caused immediate separation of *N*-phenylsydnone in 93% yield.

Support of a negative character for the preceding views on the mechanism of sydnone formation was afforded by the facts that the ethyl ester, the anilide, and the benzylamide of *N*-nitroso-*N*-phenylglycine are unaffected by hot acetic anhydride. This is to be expected, since in all three cases the cationoid properties of the carbonyl carbon atoms are largely neutralised by direct linkage with the electron-donating ethoxy-, anilino-, and benzylamino-groups respectively. It is of interest that formally the anilide and benzylamide of *N*-nitroso-*N*-phenylglycine might give rise on dehydration to cyclic meso-ionic compounds of the types (XVI) and (XVII) (R = Ph or CH_2Ph), but these modes of dehydration are excluded by the mechanism now proposed for sydnone formation, and require that, even should cyclisations occur under more drastic conditions, they should yield *N*-phenylsydnone by loss of either aniline or benzylamine.

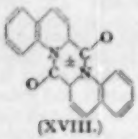


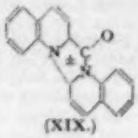
(XVI.) (XVII.)

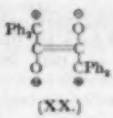
Note on the Use of the Term Meso-ionic and the Symbol $\pm$.—In Part I (*loc. cit.*, p. 311) the meaning of the term meso-ionic was applied primarily to compounds which cannot be represented even approximately by any one covalent formula, or as a hybrid of a number of covalent formulæ, but which can be depicted as a hybrid of a number of ionic (dipolar, tetrapolar, etc.) forms. Purely meso-ionic compounds already known in the cyclic series are the sydnones, the "*endo*thiodihydrothiodiazoles" and a number of closely related "*endo*" compounds (see Part I, p. 311), and probably the complex quinaldic acid derivative (XVIII) (Brown and Hammick, *Nature*, 1949, **164**, 831) and Besthorn's Red (XIX) (Krollpfeiffer and Schneider, *Annalen*, 1937, **530**, 34; see Brown and Hammick, *loc. cit.*). In the open-chain series an example of a meso-ionic compound is provided by the "dimeric diphenylketen" derived from benzilic acid, which is regarded by Schönberg and Sina (*J.*, 1947, 175) as a molecule which has possibilities of resonance and to which di- and tetra-polar forms such as (XX) contribute.

A strict application of the above definition of a meso-ionic compound would include the aliphatic diazo-compounds, the organic azides, and a number of inorganic compounds, for example, nitrous oxide, which is usually represented as a hybrid of ionic forms. It seems desirable, however, that the term "meso-ionic" and the $\pm$ symbol should not be applied to compounds unless their use obviously conveys a better understanding of the actual structure of the molecule than may be given by the more commonly used methods of description and representation. No advantage appears to be gained by classifying these compounds as "meso-ionic," although they are very simple examples of the type.

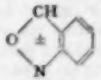
In the cyclic series the meso-ionic structure was previously represented by a single formula with the symbol ± placed within the ring, and the conversion of a bridged formula into a meso-ionic representation merely involved the replacement of the bridge bond by ±. In view of the fact that in some cases alternative hypothetical bridged structures may be drawn, it is now considered more satisfactory to represent all the atoms actually concerned in the meso-ionic part of the molecule as being united by single bonds (consisting of localised electron pairs) and then to add the symbol ± indicating the presence of mobile (π) electrons. We now prefer to represent, for example, the sydnones as in (II), and the "*endo*thiodihydrothiodiazoles" by (XXV). An advantage gained by the use of single bonds is that the resulting structure is probably as simple and satisfactory a representation of the actual molecule as may be obtained within the limits of a single, simple formula.

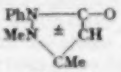

(XVIII.)


(XIX.)


(XX.)

(XXI.)


(XXII.)


(XXIII.)

Cyclic compounds such a piazthiole, benzfurazan, anthranil, etc., may be described as partially meso-ionic because they can be regarded as hybrids of both covalent (*o*-quinonoid) and ionic forms (see Part I). The expression "partially meso-ionic" is permissible just as is the term "partially aromatic"; indeed, a compound such as pyrrole may be said to be both partially meso-ionic and partially aromatic, but the former emphasises the polar, ionic nature of some of the contributing forms. It does not seem desirable to extend the idea of partially meso-ionic compounds to simple open-chain substances, for example, the amides, and in the case of the cyclic compounds mentioned above they may be represented either by *o*-quinonoid formulæ (*e.g.*, XXI, piazthiole) or by meso-ionic formulæ using the ± symbol (*e.g.*, XXII, anthranil) as seems to agree more closely with their chemical properties. The ± sign is used with single bonds in the heterocyclic rings, and can be conveniently applied to such compounds as antipyrin (see Brown, Hukins, Le Fèvre, Northcott, and Wilson, *J.*, 1949, 2812) which, if it is wished to emphasise its meso-ionic character, may be written as (XXIII).

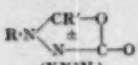
The Resonance Energy of Meso-ionic Compounds.—It has been suggested that meso-ionic compounds possess considerable resonance energy. The resonance energy of a molecule is calculated with respect to an arbitrarily chosen covalent structure, but in the case of meso-ionic compounds there is no covalent structure with which comparison can reasonably be made For example, the resonance energy of a sydnone molecule calculated with reference to the original bicyclic structure would be unsatisfactory, and it would be equally so to attempt to use any one of the ionic contributors to the hybrid as the reference state. The stability of a meso-ionic compound cannot, therefore, be readily expressed in terms of a resonance energy.

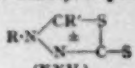
According to the molecular-orbital treatment (see Coulson, *Quart. Reviews*, 1947, **1**, 165) the stability of the sydnones and of aromatic compounds, in general, is explicable by the fact that the non-localised electrons in the molecular orbitals have higher binding energy than when paired in localised bonds, and this energy will clearly be greater in cyclic than in open-chain structures. Thus, the stability of the sydnones is due to their cyclic structure and the possession of a number of mobile (π) electrons. Calculations of the charges on the atoms composing the ring structure have been made (Longuet-Higgins, quoted by Hill and Sutton, *J.*, 1949, 752; *J. Chim. physique*, 1949, **46**, 247), and it is possible that a more accurate picture of the actual state of the molecule may thus be obtained than is possible by assessing the relative probabilities of the canonical forms contributing to the hybrid and arriving at a weighted mean value for the charge distribution. The latter method has, however, much to commend it to the organic chemist, and applied with proper knowledge and caution may lead to a moderately accurate picture of the charge distribution, and hence to a rough idea of the magnitude and direction of the dipole moment of the molecule. It may be pointed out here that a meso-ionic

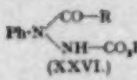
structure is not necessarily associated with a high dipole moment, as is the case with the sydnones and many closely related compounds; the moment may even be zero, as should be the case with the quinaldic acid derivative (XVIII). Professor H. D. Springall and Mr. C. B. Knowles have determined the heats of combustion of certain sydnones at the University of Manchester, and the results of their work will be published shortly.

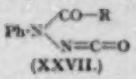
Attempts to prepare Cyclic Meso-ionic Compounds of Type (XXIV).—A possible cyclic meso-ionic system is shown in formula (XXIV), which differs from the sydnones in the reversal of the $-CO\cdot O-$ grouping. The dithio-analogues (XXV) are known (see Schönberg, *J.*, 1938, 824; Jensen and Friediger, *Kgl. Danske Videnskab. Selskab*, 1943, **20**, 1; Earl, Leake, and Le Fèvre, *J.*, 1948, 2273; this series, Part I, *loc. cit.*). Our attempted syntheses of (XXIV) are mainly based on methods by which the dithio-analogues have been prepared, and failure is due in several cases to the instability of carbamic acids.

(1) Compounds of type (XXV) are formed from acid chlorides and salts of *N'*-dithiocarboxy-*N*-arylhydrazines (Busch *et al.*, *J. pr. Chem.*, 1899, **60**, 218, 228, 231; 1903, **67**, 201, 202, 250, 257). The potassium salt of *N'*-carboxy-*N*-phenylhydrazine reacted with acid chlorides to give only mixtures of *N*- and *N'*-acyl- and *NN'*-diacyl-*N*-phenylhydrazines. In attempts to prepare the *N'*-carboxy-*N*-acyl-*N*-phenylhydrazines, the *N*-formyl-, *N*-acetyl- (Heller, *Annalen*, 1891, **263**, 281), and *N'*-carbethoxy-*N*-benzoyl-*N*-phenylhydrazines (XXVI; R = H, Me, and Ph) were subjected to cold alkaline hydrolysis, but *N*-acylhydrazines resulted through loss of carbon dioxide. Again, *N*-benzoyl-*N*-phenylhydrazine did not undergo carboxylation with


(XXIV.)


(XXV.)


(XXVI.)


(XXVII.)

carbon dioxide in ethereal solution (cf. the carboxylation of phenylhydrazine; E. Fischer, *Annalen*, 1878, **190**, 123; Busch and Stern, *J. pr. Chem.*, 1899, **60**, 236). (2) *iso*Cyanates (XXVII) might cyclise to compounds (XXIV), but *N*-benzoyl-*N'*-carbethoxy-*N*-phenylhydrazine (XXVI; R = Ph) did not yield an *iso*cyanate by reaction with phosphoric anhydride, and the hydrochloride of *N*-benzoyl-*N*-phenylhydrazine reacted with carbonyl chloride giving the urea derivative $(Ph\cdot CO\cdot NPh\cdot NH)_2CO$. (3) Benzimino ethyl ether hydrochloride and the potassium salt of *N'*-carboxy-*N*-phenylhydrazine gave carbon dioxide and *N*-anilinobenzamidine, $Ph\cdot C(:NH)\cdot NH\cdot NHPh$, isolated as its picrate [cf. the corresponding synthesis of (XXV), Busch and Schneider, *J. pr. Chem.*, 1903, **67**, 246]. (4) The dithio-compounds (XXV; R = H) are formed from sodium dithioformate and the potassium salts of *N'*-dithiocarboxy-*N*-arylhydrazines (unpublished observation), but the reaction of sodium dithioformate with the potassium salt of *N'*-carboxy-*N*-phenylhydrazine gave only *N'*-thioformyl-*N*-phenylhydrazine, $Ph\cdot NH\cdot NH\cdot CHS$.

Experimental.

Methyl α-Chloro-p-chlorophenylacetate.—Phosphorus pentachloride (42 g.) and *p*-chloromandelic acid (18·5 g.; Jenkins, *J. Amer. Chem. Soc.*, 1931, **53**, 2341) were heated on the steam-bath for ½ hour, and then refluxed (oil-bath) for 3 hours. After cooling, the mixture was treated with methanol (400 c.c.), diluted with water, and extracted with ether. The extract was washed with aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and distilled, giving *methyl α-chloro-p-chlorophenylacetate* (17 g., 79%), b. p. 140—143°/16 mm. (Found: C, 49·7; H, 3·8. $C_9H_8O_2Cl_2$ requires C, 49·4; H, 3·7%).

α-Anilino-p-chlorophenylacetic Acid.—Methyl α-chloro-*p*-chlorophenylacetate (20 g.), aniline (5·8 c.c.), hydrated sodium acetate (12·5 g.), and methanol (20 c.c.) were refluxed at 125—130° for 5 hours, cooled, poured into water (500 c.c.), and extracted with ether. The extract yielded methyl α-anilino-*p*-chlorophenylacetate, b. p. 165°/1 mm. (slight decomp.), which was characterised as the *toluene*-p-*sulphonyl* derivative, colourless tablets (from methanol), m. p. 137° (Found: C, 61·3; H, 4·8. $C_{22}H_{20}O_4NClS$ requires C, 61·4; H, 4·7%). The α-anilino-ester was hydrolysed by boiling it with excess of 10% aqueous sodium hydroxide for ½ hour, and the filtered solution yielded on acidification *α-anilino-p-chlorophenylacetic acid* which separated from aqueous ethanol as small needles, m. p. 178° (decomp.) (14 g., 59%) (Found: C, 64·0; H, 4·5; N, 4·8; Cl, 13·8. $C_{14}H_{12}O_2NCl$ requires C, 64·3; H, 4·6; N, 5·4; Cl, 13·6%).

N-Phenyl-C-p-chlorophenylsydnone.—Sodium nitrite (1·75 g.) was added with stirring to a solution of α-anilino-*p*-chlorophenylacetic acid (6 g.) in concentrated sulphuric acid (90 c.c.) at 0°, and after 1½ hours the mixture was poured on to ice. The crude nitroso-acid was extracted into ether, acetic anhydride (20 c.c.) added to the dried ($MgSO_4$) extract, and the solution heated on the water-bath for ½ hour after removal of the ether by distillation. The solid precipitated by the addition of water was washed with sodium carbonate solution, and crystallised from aqueous ethanol, giving *N-phenyl-C-p-chlorophenylsydnone* (4·4 g., 71%) as fine, faintly yellow needles, m. p. 129° (decomp.) (Found: C, 61·5; H, 3·3; N, 10·2; Cl, 13·4. $C_{14}H_9O_2N_2Cl$ requires C, 61·7; H, 3·3; N, 10·3; Cl, 13·0%). It shows a weak greenish-white fluorescence in ultra-violet light.

Methyl α-Bromo-p-chlorophenylacetate.—*p*-Chlorobenzyl cyanide (95 g.; Jackson and Field, *Amer.*

Chem. J., 1886, **2**, 89) was hydrolysed by boiling it for 2½ hours with acetic acid, water, and concentrated sulphuric acid (75 c.c. each). The isolated *p*-chlorophenylacetic acid (101 g.; m. p. 103—104°; lit., m. p. 103·5—104°) was converted into *p*-chlorophenylacetyl chloride (35 g.; b. p. 113°/16 mm.) by refluxing it with thionyl chloride (100 g.) and pyridine (1 c.c.) for 5 hours and fractionating the product. To this acid chloride was added anhydrous bromine (10 c.c.), whilst stirring and irradiating the mixture with ultra-violet light during ½ hour, the temperature then being slowly raised to 60°, where it was maintained for 3 hours. The resulting crude bromo-acid chloride was cautiously added to absolute methanol, the excess of which was then removed. The residual oil was dissolved in ether, washed with aqueous sodium carbonate, dried, and distilled, giving *methyl α-bromo-p-chlorophenylacetate* (36·4 g., 75%), b. p. 149—153°/16 mm., 128—129°/3 mm. (Found: C, 41·5; H, 3·5. $C_9H_8O_2BrCl$ requires C, 41·6; H, 3·1%).

Methyl α-p-Chloroanilino-p-chlorophenylacetate.—Methyl α-bromo-*p*-chlorophenylacetate (20 g.), *p*-chloroaniline (9·7 g.), hydrated sodium acetate (10·3 g.), and absolute ethanol (20 c.c.) were heated at 135—140° for 5 hours, and the product isolated as in the previous case. *Methyl α-p-chloroanilino-p-chlorophenylacetate* (19·0 g., 81%) was obtained as colourless needles, m. p. 129°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 58·1; H, 4·2; N, 4·6; Cl, 22·9. $C_{15}H_{13}O_2NCl$ requires C, 58·1; H, 4·2; N, 4·5; Cl, 22·9%). This compound was also obtained in a similar manner from methyl α-chloro-*p*-chlorophenylacetate.

α-p-Chloroanilino-p-chlorophenylacetic Acid.—Hydrolysis of the preceding ester with 10% aqueous sodium hydroxide for ½ hour gave the *acid* (98% yield) as colourless needles (from ethanol), m. p. 164° (decomp.) (Found: C, 57·2; H, 3·7; N, 4·6; Cl, 23·4. $C_{14}H_{11}O_2NCl_2$ requires C, 56·8; H, 3·7; N, 4·7; Cl, 24·0%). When dried for analysis at 80° under diminished pressure the crystals became opaque.

NC-*Di-p-chlorophenylsydnone.*—Nitrosation of the preceding acid (9 g.) was effected in concentrated sulphuric acid (100 c.c.) by the addition of sodium nitrite (2·3 g.) at 0°, addition of the mixture to ice after 1½ hours, and extraction into ether. The extract was dried ($MgSO_4$), acetic anhydride (60 c.c.) added, and after 48 hours at room temperature the solvent was removed, the residue heated on the steam-bath for 5 minutes (longer heating results in the formation of dark material), water added, and the solid collected, washed with sodium carbonate solution, and crystallised from ethanol. NC-*Di-p-chlorophenylsydnone* (4·8 g., 51%) was obtained as almost colourless plates, m. p. 144° (Found: C, 54·6; H, 2·7; N, 9·5; Cl, 23·3. $C_{14}H_7O_2N_2Cl_2$ requires C, 54·7; H, 2·6; N, 9·1; Cl, 23·1%), which exhibit a marked greenish-white fluorescence in ultra-violet light.

*Methyl α-Chloro-*p*-tolylacetate.*—*p*-Methylmandelic acid (62 g.), prepared from *p*-tolualdehyde (99 g.) by the method given by Jenkins (*loc. cit.*) for the preparation of *p*-chloromandelic acid, was added to phosphorus pentachloride (160 g.), and after the vigorous reaction had subsided the mixture was refluxed for 3 hours, cooled, and added to methanol (1 l.). The solution was then diluted with water and extracted with ether, the extract shaken with sodium hydrogen carbonate solution, dried, and distilled, giving *methyl α-chloro-p-tolylacetate* (45 g., 61%), b. p. 130—140°/13 mm. (Found: C, 60·5; H, 5·3; Cl, 17·2. $C_{10}H_{11}O_2Cl$ requires C, 60·5; H, 5·6; Cl, 17·8%).

α-Anilino-p-tolylacetic Acid.—The preceding ester (20 g.), aniline (9·4 g.), hydrated sodium acetate (14 g.), and methanol (20 c.c.) were refluxed for 5 hours and poured into water (100 c.c.). Extraction with ether gave impure methyl α-anilino-*p*-tolylacetate (24 g.), which could not be distilled without decomposition but gave a *toluene-p-sulphonyl* derivative separating from aqueous methanol in colourless bipyramids, m. p. 109—110° (Found: C, 67·6; H, 5·0. $C_{23}H_{23}O_4NS$ requires C, 67·5; H, 5·6%). Alkaline hydrolysis of the crude ester (20 g.) as in the previous cases gave *α-anilino-p-tolylacetic acid* (14 g.), small, colourless needles (from aqueous methanol), m. p. 151—152° (Found: C, 73·9; H, 5·9; N, 5·8. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·3; N, 5·8%).

N-*Phenyl-C-p-tolylsydnone.*—Nitrosation of the preceding acid (7·5 g.) in concentrated sulphuric acid (80 c.c.) with sodium nitrite (2·25 g.), and treatment of the nitroso-acid in ether with acetic anhydride (50 c.c.), as in the case of *N*-phenyl-*C*-*p*-chlorophenylsydnone, gave *N-phenyl-C-p-tolylsydnone* (5·1 g., 65%), light yellow needles (from ethanol), m. p. 144·5—146° (Found: C, 71·0; H, 4·6; N, 10·9. $C_{15}H_{12}O_2N_2$ requires C, 71·4; H, 4·8; N, 11·1%). It shows a weak greenish-white fluorescence in ultra-violet light.

Methyl α-p-Toluidino-p-tolylacetate.—Reaction of methyl α-chloro-*p*-tolylacetate (20 g.) with *p*-toluidine (10·8 g.), as in the preparation of methyl α-anilino-*p*-tolylacetate, gave *methyl α-p-toluidino-p-tolylacetate* (14·5 g., 43%), as tablets, m. p. 60—60·5°, from aqueous methanol (Found: C, 76·1; H, 6·8; N, 5·2. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1; N, 5·2%).

α-p-Toluidino-p-tolylacetic Acid.—Alkaline hydrolysis of the preceding ester (12·2 g.) gave the *acid* (9 g., 78%) as small needles, m. p. 153°, from aqueous ethanol (Found: C, 75·0; H, 6·2; N, 5·6. $C_{16}H_{17}O_2N$ requires C, 75·3; H, 6·7; N, 5·5%).

NC-*Di-p-tolylsydnone.*—The nitroso-acid obtained from the preceding acid (6·7 g.), concentrated sulphuric acid (100 c.c.), and sodium nitrite (2 g.), as in previous cases, was extracted into ether, the extract dried, and acetic anhydride (40 c.c.) added. The ether was removed by distillation, the residue heated on the steam-bath for 5 minutes, cooled rapidly, and poured into water, and the solid collected, washed with water and aqueous sodium carbonate, triturated with ether, and finally crystallised from ethanol. The *NC-di-p-tolylsydnone* formed colourless needles (5·2 g., 74%), m. p. 156—157·5° (decomp.) (Found: C, 72·0; H, 5·1; N, 10·7. $C_{16}H_{14}O_2N_2$ requires C, 72·1; H, 5·3; N, 10·5%). It exhibits a marked greenish-white fluorescence in ultra-violet light.

Ethyl β-Anilinopropionate.—Ethyl β-chloropropionate (36 g.), aniline (50 c.c.), hydrated sodium acetate (36 g.), and ethanol (10 c.c.) were heated at 125—130° for 12 hours. Water (100 c.c.) was added, and the oil taken up in ether, washed with 2N-sodium hydroxide (100 c.c.), dried ($MgSO_4$), and distilled, giving ethyl β-anilinopropionate (38 g., 75%) as a colourless oil, b. p. 125°/2 mm. (this ester, b. p. 175°/18 mm., was previously prepared by de Mouilpied, *J.*, 1905, **87**, 441, from β-iodopropionic ester and aniline).

β-Anilinopropionic Acid.—Ethyl β-anilinopropionate (40 g.), sodium hydroxide (12·5 g.), water (125 c.c.), and ethanol (10 c.c.) were refluxed for ½ hour, cooled, acidified to pH 4 with concentrated

hydrochloric acid, and kept overnight at 0°. The β-anilinopropionic acid (24·2 g., 70%) was used directly for the nitrosation. Crystallisation from benzene–light petroleum (b. p. 60—80°) gave the pure acid as plates, m. p. 59° (Bischoff and Mintz, *Ber.*, 1892, **25**, 2351, prepared the acid from β-iodopropionic acid and aniline and give m. p. 59—60°).

N-Nitroso-β-anilinopropionic Acid (III).—A solution of sodium nitrite (13·5 g.) in water (100 c.c.) was slowly added at 0° to β-anilinopropionic acid (32 g.) suspended in water (400 c.c.). After 1½ hours the mixture was stirred with charcoal, filtered, and acidified with hydrochloric acid, and the crystalline precipitate was collected after being kept overnight at 0°, washed, and dried (yield: 33·7 g., 90%). Crystallisation from aqueous ethanol gave *N-nitroso-β-anilinopropionic acid* as almost colourless needles, m. p. 77° (Found: C, 55·9; H, 5·2; N, 14·7. $C_9H_{10}O_3N_2$ requires C, 55·7; H, 5·2; N, 14·4%).

C-Chloro-N-phenylsydnone.—Chlorine (4·4 g.) was passed into a solution of *N*-phenylsydnone (10 g.) in pure acetic anhydride (100 c.c.) at 0°, the solvent removed under diminished pressure, and the residue washed with ethanol and crystallised from 50 c.c. of ethanol. *C*-Chloro-*N*-phenylsydnone (4 g.) was obtained as colourless needles, m. p. 128·5° (Found: C, 49·1; H, 2·7; N, 14·0; Cl, 18·3. Calc. for $C_8H_5O_2N_2Cl$: C, 48·9; H, 2·5; N, 14·3; Cl, 18·1%). Eade and Earl chlorinated the sydnone in acetic acid in presence of sodium acetate, and obtained the chloro-compound, m. p. 127°, which was incompletely analysed.

C-Chloro-N-p-chlorophenylsydnone.—Reaction of chlorine (2·6 g.) with *N*-p-chlorophenylsydnone (7 g.) in acetic anhydride (120 c.c.) gave, by the previous procedure, *C-chloro-N-p-chlorophenylsydnone* (4·2 g., 51%) as faintly yellow needles, m. p. 108° (decomp.) from ethyl alcohol (Found: C, 41·6; H, 1·7; N, 12·2; Cl, 30·4. $C_8H_4O_2N_2Cl_2$ requires C, 41·6; H, 1·8; N, 12·1; Cl, 30·7%).

C-Nitro-N-phenylsydnone.—*N*-Phenylsydnone (3·6 g.) in concentrated sulphuric acid (15 c.c.) was stirred at −10° during the dropwise addition of a mixture of concentrated nitric acid (2 c.c.) and sulphuric acid (3 c.c.). The mixture was then stirred for ½ hour and poured on ice, and the solid collected, washed with aqueous sodium hydrogen carbonate and water, and crystallised from aqueous dioxan. *C-Nitro-N-phenylsydnone* (1·1 g., 24%) separated as light yellow plates, m. p. 142° (Found: C, 46·4; H, 2·4. $C_8H_5O_4N_3$ requires C, 46·4; H, 2·4%). This compound is rather unstable, cannot be crystallised from alcohol, and undergoes general decomposition when heated with dilute acids. In comparison, the *N-o-*, *-m-*, and *-p*-nitrophenylsydnones may be readily recrystallised, and yield the nitrophenylhydrazines on acid hydrolysis.

Benzylamide of N-Nitroso-N-phenylglycine (IV; R = Ph, R′ = H).—(a) *From N-phenylsydnone.* A mixture of *N*-phenylsydnone (5 g.) and benzylamine (7·5 c.c.) was heated at 120° for 8 hours and then poured into water. The precipitate (8 g., 96%) was collected, dried, washed with a little ether, and recrystallised several times from ethanol. The *benzylamide* of *N*-nitroso-*N*-phenylglycine separated in almost colourless needles, m. p. 109—110° (Found: C, 66·6; H, 5·5; N, 15·8. $C_{15}H_{15}O_2N_3$ requires C, 66·9; H, 5·6; N, 15·6%). It gave a positive Liebermann nitroso-reaction.

(b) *By nitrosation of the benzylamide of N-phenylglycine.* Sodium nitrite (6·33 g.) was slowly added to a stirred solution of the benzylamide of *N*-phenylglycine (see below) (20 g.) in concentrated sulphuric acid (200 c.c.) at 0—5°. After 2 hours it was poured on crushed ice (500 g.) and water (250 c.c.), and the precipitate was collected, washed and dried (19·0 g., 85%). Crystallisation from ethanol (50 c.c.) gave the benzylamide of *N*-nitroso-*N*-phenylglycine as colourless needles, m. p. and mixed m. p. 110·5° (Found: C, 67·0; H, 5·8; N, 15·3%).

Benzylamide of N-Phenylglycine.—*N*-Phenylglycine ethyl ester (15 g.) and benzylamine (25 c.c.) were kept at 140° for 8 hours and then poured into water, and the solid was collected, washed with dilute hydrochloric acid, and dried. The benzylamide of *N*-phenylglycine (18·8 g., 94%) separated from ethanol or benzene as colourless plates, m. p. 114° (Found: C, 74·8; H, 6·7; N, 11·8. Calc. for $C_{15}H_{16}ON_2$: C, 75·0; H, 6·7; N, 11·7%) (Dermer and King, *J. Org. Chem.*, 1943, **8**, 169, prepared this compound from *N*-phenylglycine and gave m. p. 113—114°). The *toluene-p-sulphonyl* derivative forms colourless needles, m. p. 138°, from ethanol (Found: C, 67·3; H, 5·6; N, 7·4; S, 8·4. $C_{22}H_{22}O_3N_2S$ requires C, 67·0; H, 5·6; N, 7·1; S, 8·1%).

Benzylamide of N-Nitroso-N-benzylglycine (IV; R = CH_2Ph, R′ = H).—Reaction of *N*-benzylsydnone (3 g.) with benzylamine (5 c.c.) was carried out as with *N*-phenylsydnone (above), and yielded the *benzylamide* of *N*-nitroso-*N*-benzylglycine as colourless needles (2·7 g., 56%), m. p. 110·5°, from ethanol (Found: C, 67·9; H, 6·1; N, 14·8. $C_{16}H_{17}O_2N_3$ requires C, 67·8; H, 6·0; N, 14·8%).

Benzylamide of N-Nitroso-N-cyclohexylglycine (IV; R = C_6H_{11}, R′ = H).—*N-cyclo*Hexylsydnone (3 g.) and benzylamine (9 c.c.) gave, as in the previous cases, the *benzylamide* of *N*-nitroso-*N-cyclo*hexylglycine as colourless needles (1·4 g., 29%), m. p. 130·5—131°, from ethanol (Found: C, 65·5; H, 7·6; N, 14·9. $C_{15}H_{21}O_2N_3$ requires C, 65·5; H, 7·7; N, 15·3%).

Benzylamide of N-Nitroso-α-anilinophenylacetic Acid (IV; R = R′ = Ph).—A mixture of *NC*-diphenylsydnone (3 g.) and benzylamine (10 c.c.) was heated at 125° for 14 hours and then poured into water. The solid (3·85 g., 89%) was collected, washed with light petroleum, and crystallised from benzene–light petroleum (b. p. 60—80°) (50 c.c.) and then from ethanol, giving the *benzylamide* (2·1 g.) of *N*-nitroso-α-anilinophenylacetic acid as almost colourless needles, m. p. 142·5° (Found: C, 72·8; H, 5·6; N, 12·4. $C_{21}H_{19}O_2N_3$ requires C, 73·1; H, 5·5; N, 12·2%).

Preparation of N-Phenylsydnone from the Potassium Salt of N-Nitroso-N-phenylglycine.—The potassium salt of *N*-nitroso-*N*-phenylglycine (0·5 g.), prepared by the addition of alcoholic potassium hydroxide to *N*-nitroso-*N*-phenylglycine dissolved in the minimum quantity of ethyl alcohol, and acetic anhydride (15 c.c.) were heated on a steam-bath till complete dissolution occurred. The cooled, filtered solution was evaporated under diminished pressure, and the residue washed with water and crystallised from water, giving *N*-phenylsydnone, m. p. and mixed m. p. 134° (0·34 g., 91%). A similar result was obtained when 1 equivalent of acetyl chloride was added to the mixture, but dissolution occurred immediately and the reaction time was reduced to 1 hour.

Mixed Anhydride of N-Nitroso-N-phenylglycine and Acetic Acid (VIII).—Pure acetyl chloride (0·33 c.c.) in dry benzene (2 c.c.) was added to the finely powdered potassium salt of *N*-nitroso-*N*-phenylglycine (1·01 g.) in dry benzene (10 c.c.) with vigorous stirring at 10°. After 1 hour the filtered solution

was evaporated under diminished pressure, leaving a thick oil (0·75 g.) which slowly solidified at 0° to a crystalline mass, m. p. 40—42°. Recrystallisation of a portion was effected by adding light petroleum (b. p. 40—60°) to its solution in benzene and cooling to 0°, the *mixed anhydride* of *N*-nitroso-*N*-phenylglycine and acetic acid separating as long, colourless needles, m. p. 45·5—46·0° (Found, in material analysed within 1 hour of collection: N, 12·7. $C_{10}H_{10}O_4N_2$ requires N, 12·6%).

When kept at 5° this compound developed a strong smell of acetic acid (Found, after 12 hours: N, 13·4%), and the m. p. rose to *ca.* 129° after 5 days. Yields of 75—80% of *N*-phenylsydnone were thus obtained, but slight decomposition of the sydnone occurs by long storage in contact with acetic acid, and the best conversion occurred by keeping the substance under diminished pressure over potassium hydroxide. After 5—6 days the solid (m. p. 131°) was washed with a little ether and dried, and then had m. p. and mixed m. p. with *N*-phenylsydnone 135°.

N-Phenylsydnone (0·20 g., 85%; m. p. 131—134°) was also obtained by refluxing the mixed anhydride (0·32 g.) in dry benzene (5 c.c.) for 6 hours.

Reaction of Thionyl Chloride with N-Nitroso-N-phenylglycine.—(*a*) To *N*-nitroso-*N*-phenylglycine (2 g.) in dry ether (20 c.c.) was added pure thionyl chloride (1·32 g.) in dry ether (5 c.c.). After a few minutes *N*-phenylsydnone began to separate in colourless needles. When this material showed signs of discoloration the ethereal layer was decanted, the solid washed with a little ether and then dilute sodium hydrogen carbonate solution, collected, and dried (0·5 g., 28%; m. p. 132—135°, undepressed when mixed with *N*-phenylsydnone).

(*b*) Pure thionyl chloride (1·32 g.) in dry dioxan (2 c.c.) was added slowly, with occasional cooling in ice, to a solution of *N*-nitroso-*N*-phenylglycine (2 g.) in a mixture of dioxan (5 c.c.) and pyridine (2·7 c.c.). After 0·25 hour at room temperature the solution was poured into water (150 c.c.), the solid collected, washed with dilute sodium hydrogen carbonate solution and then water, and dried (yield: 1·35 g., 76%); it had m. p. and mixed m. p. with *N*-phenylsydnone, 134—135°.

Reaction of Trifluoroacetic Anhydride with N-Nitroso-N-phenylglycine.—*N*-Nitroso-*N*-phenylglycine (1·0 g.) was dissolved in dry ether (10 c.c.), and trifluoroacetic anhydride (1·0 c.c.) added at −5°. *N*-Phenylsydnone separated immediately and, after removal of volatile compounds under reduced pressure, was washed with dilute aqueous sodium hydrogen carbonate and then with water, and dried (yield: 0·84 g., 93%); it had m. p. and mixed m. p. 135—136°.

Anilide of N-Phenylglycine.—When chloroacetyl chloride (50 g.) in ether (100 c.c.) was added to a solution of aniline (182 c.c.) in ether (500 c.c.) (cf. Meyer, *Ber.*, 1875, **8**, 1153) it yielded both the chloroacetyl derivative of aniline (53 g.; m. p. 133°, from ethanol) and the anilide of *N*-phenylglycine (37 g.; m. p. 111°, from water). The former was converted into the latter (92% yield) by reaction with aniline and sodium acetate in ethanol (Meyer, *loc. cit.*).

Anilide of N-Nitroso-N-phenylglycine.—Sodium nitrite (6·7 g.) was added with stirring to a solution of the preceding anilide (20 g.) in concentrated sulphuric acid (200 c.c.) at 0°. After 1½ hours the mixture was poured into crushed ice (500 g.) and water (200 c.c.), the precipitate collected, washed, and crystallised from dilute ethanol (yield 18·4 g.) and then from ethanol (charcoal), giving the *anilide* of *N*-nitroso-*N*-phenylglycine as straw-coloured needles, m. p. 144° (Found: C, 65·9; H, 5·0; N, 16·4. $C_{14}H_{13}O_3N_3$ requires C, 65·9; H, 5·1; N, 16·5%).

N-Benzylsydnone.—The yield of *N*-benzylsydnone from *N*-nitroso-*N*-benzylglycine (40 g.), inadvertently omitted in Part I, was 33·9 g. (94%).

N'-Carbethoxy-N-benzoyl-N-phenylhydrazine (XXVI; R = Ph).—*N'*-Carbethoxy-*N*-phenylhydrazine (10 g.; Heller, *Annalen*, 1891, **263**, 278), benzoyl chloride (7·8 g.), and pyridine (30 c.c.) were heated on the steam-bath for 2 hours, water was added, and the solid was collected. Recrystallisation from benzene–light petroleum (b. p. 60—80°) gave *N'-carbethoxy-N-benzoyl-N-phenylhydrazine* as needles, m. p. 128° (5·2 g., 33%) (Found: C, 67·6; H, 5·6; N, 10·4. $C_{16}H_{16}O_3N_2$ requires C, 67·6; H, 5·7; N, 9·9%).

N'-Carbethoxy-N-formyl-N-phenylhydrazine (XXVI; R = H).—A mixture of *N'*-carbethoxy-*N*-phenylhydrazine (10 g.) and 70% formic acid (80 c.c.) was heated on the steam-bath for 1½ hours, poured into water (200 c.c.), neutralised with sodium hydroxide solution, and extracted with ether. The extract was dried ($MgSO_4$) and evaporated, giving *N'-carbethoxy-N-formyl-N-phenylhydrazine* as needles [from benzene–light petroleum (b. p. 60—80°)], m. p. 85° (9·6 g., 83%) (Found: C, 57·8; H, 5·9; N, 13·5. $C_{10}H_{12}O_3N_2$ requires C, 57·7; H, 5·8; N, 13·5%).

Reaction between N-Benzoyl-N-phenylhydrazine Hydrochloride and Carbonyl Chloride.—*N*-Benzoyl-*N*-phenylhydrazine hydrochloride (4·9 g.) was prepared by hydrolysis of *N*-benzoyl-*N'*-acetyl-*N*-phenylhydrazine (5 g.; Widman, *Ber.*, 1893, **26**, 947) with concentrated hydrochloric acid (7·5 c.c.), water (30 c.c.), and ethanol (15 c.c.) on the steam-bath for 3 hours and evaporation to dryness. The hydrochloride (5 g.) and a 12·5% w/w solution (40 c.c.) of carbonyl chloride in toluene were refluxed with vigorous stirring until evolution of hydrogen chloride ceased (*ca.* 5 hours). The solid which separated on cooling (3·7 g.) was crystallised from nitrobenzene, giving needles of *NN'-di(benzanilido)urea*, $(Ph{\cdot}CO{\cdot}NPh{\cdot}NH)_2CO$, m. p. 274° (decomp.) (Found: C, 72·0; H, 4·9; N, 12·6. $C_{31}H_{26}O_3N_4$ requires C, 72·0; H, 4·9; N, 12·4%).

Reaction of Benziminoethyl Ether Hydrochloride with the Potassium Salt of N'-Carboxy-N-phenylhydrazine.—The potassium salt of *N'*-carboxy-*N*-phenylhydrazine (5 g.; Fischer, *Annalen*, 1878, **190**, 123; Busch and Stern, *J. pr. Chem.*, 1899, **60**, 236) was vigorously stirred in ethanol (100 c.c.) at −10°, and benziminoethyl ether hydrochloride added slowly. After 2 hours the mixture was allowed to warm to room temperature and then evaporated to dryness under reduced pressure in an atmosphere of nitrogen. Ether (100 c.c.) was now added, the extract evaporated, and the residual oil which solidified on trituration with light petroleum (b. p. 60—80°) was washed with light petroleum and dried [yield, 3·8 g.; m. p. 90—94° (decomp.)]. This basic material was unstable and could not be recrystallised; it gave a bright yellow *picrate*, m. p. 199° (decomp.), as needles from ethanol (Found: C, 51·8; H, 3·7; N, 19·1. $C_{19}H_{15}O_7N_7$ requires C, 51·8; H, 3·7; N, 19·1%). The free base, $C_{13}H_{13}N_3$, is presumably *N*-anilinobenzamidine, previously described by Voswinckel (*Ber.*, 1903, **36**, 2484) as an unstable oil.

Reaction of Sodium Dithioformate with the Potassium Salt of N'-Carboxy-N-phenylhydrazine.—To a

solution of the potassium salt of *N'*-carboxy-*N*-phenylhydrazine (10 g.) in water (50 c.c.) was added a solution of sodium dithioformate (11 g.) in water (50 c.c.). After 48 hours the purple oil which later solidified was collected and dried (5·1 g.). It crystallised from light petroleum (b. p. 60—80°), giving *N'*-thioformyl-*N*-phenylhydrazine as thick colourless needles, m. p. 39·5—41°, undepressed on admixture with *N'*-thioformyl-*N*-phenylhydrazine, m. p. 39·5—41°, prepared similarly from phenylhydrazine and sodium dithioformate (Baker, Ollis, and Poole, forthcoming publication).

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321. *Reduction by Dissolving Metals. Part VII. The Reactivity of Mesomeric Anions in Relation to the Reduction of Benzene Rings.*

By ARTHUR J. BIRCH.

The equilibrium between 2 : 5- (I) and 2 : 3-dihydroanisole (III), set up through their potassium salt (II), is investigated in liquid ammonia solution, and the conditions are defined for the interconversion of the two isomers. Some reactions of the dipotassium salts derived by the action of potassium amide in ammonia on several 1 : 4-dihydrobenzoic acids, several $\alpha\beta$-unsaturated aliphatic acids, and several arylacetic acids are investigated; in particular methyl iodide is found to introduce one or two methyl groups on to the carbon atom adjacent to the carboxyl group. Several 2 : 5-dihydroanisole derivatives are similarly methylated in the 2-position, and a methyl or a 2-phenylethyl group is introduced into the 2-position of 1 : 3-dimethoxy-2 : 5-dihydrobenzene.

Some generalisations on the reactivity of mesomeric anions are applied to explain the positions taken up by the hydrogen atoms added to substituted benzene rings by means of sodium and alcohols in liquid ammonia.

THE hydrogenation of an aromatic system by a dissolving metal proceeds by electron and proton addition in what may be considered as successive or simultaneous stages according to conditions, since a series of equilibria is involved: $M + 2e \rightleftharpoons M^{-\bullet} + e \rightleftharpoons M^{--} \longrightarrow MH_2$ (M = an aromatic molecule throughout this paper), and, under the right pH conditions, $M^{-\bullet} + H^+ \rightleftharpoons MH^\bullet$ (Birch, *Quart. Rev.*, 1950, **4**, 69, *q.v.* for references to any undocumented statements in the present paper).† The rate- or potential-determining stage appears from polarographic and other evidence to be the addition of the first electron. The addition of the second electron appears to be slow by comparison, although chemical evidence is available that this stage is at least chemically reversible. The slowness is understandable, because the reaction is between two negatively charged particles, a radical-anion and a solvated electron. The reduction process can be pictured as the rapid and reversible addition of an electron, the position of equilibrium being governed in the usual manner by the free-energy difference between M and $M^{-\bullet}$, followed by further reactions which are either irreversible or slow to attain equilibrium. The rate, or the potential at which reduction occurs at any given rate, thus depends chiefly on the concentration of $M^{-\bullet}$, and hence on the free-energy difference. This difference can be calculated in a semi-quantitative manner from bond-energy and resonance-energy changes which are considered in more detail elsewhere (cf. Birch, *loc. cit.*).

In the reduction of aromatic compounds containing benzene rings the primary reduction product, defined for convenience as the first non-ionic product which can be isolated, contains two added hydrogen atoms and thus corresponds to the addition of two electrons and two protons. With polycyclic compounds, or benzoic acids, these additions can be made to take place in two separate stages, the salt of the di-anion, *e.g.*, $2Na^+M^{--}$, being stable in ammonia at about −70° (*e.g.*, Hückel and Bretschneider, *Annalen*, 1937, **540**, 157). With a molecule containing one isolated benzene ring such successive addition is not possible, and reduction occurs only by the simultaneous action of the metal and an alcohol in ammonia. This must be caused by the addition of protons from the alcohol either to M^{--} or to the less strongly basic $M^{-\bullet}$, followed in the latter case by the addition of another electron and another proton. The equilibria above are thus caused to proceed in the direction of formation of stable hydrogenation

† The signs $^-$ and $^\bullet$ here represent two and one unshared electrons respectively.

products, even though the instantaneous concentration of ions may be very small because of the small free-energy change in the process of electron-addition.

Whichever route is followed, it is evident that a reduction intermediate is the mesomeric univalent anion MH^-: $M^{\cdot-} + H^+ \longrightarrow MH^-$, or $M^{-\bullet} + H^+ \longrightarrow MH^\bullet + e \longrightarrow MH^-$. There are at least two positions in such ions where proton-addition can occur, and in the case of benzene rings (*e.g.*, II) there are three positions. A study of their reactivity is therefore fundamental for an understanding of the relative positions of the hydrogen atoms added to the ring. Reactivity is experimentally found to be in the $\alpha\delta$-positions [*e.g.*, anisole $\longrightarrow$ 2 : 5-dihydroanisole (I)] with sodium–alcohol–ammonia solutions (*e.g.*, Part I, *J.*, 1944, 430), although with calcium hexammoniate the $\alpha\beta$-dihydro-derivatives appear to be intermediates which are further reduced because they contain conjugated double bonds (*e.g.*, Part V, *J.*, 1947, 1642). An examination has accordingly now been made of the addition of protons to several types of mesomeric anion, such as (II), under conditions where the process is reversible and irreversible, *i.e.*, when the proton-donor is a much stronger acid than the conjugate acid from the ion, and when it is of about the same strength. For the reduction of benzene rings these conditions hold when the proton donor is alcohol (pK about 18) (irreversible addition) and when it is ammonia (pK about 34) (reversible addition).

It has already been briefly pointed out that the constitution of the product depends on whether the addition of protons to an anion is reversible or irreversible (Birch, *Faraday Soc. Discussion*, 1947, **2**, 246; cf. Catchpole, Hughes, and Ingold, *J.*, 1948, 8). Under reversible conditions an equilibrium is set up, such as (i), where A^- and B^- are the canonical forms defining the mesomeric anion:

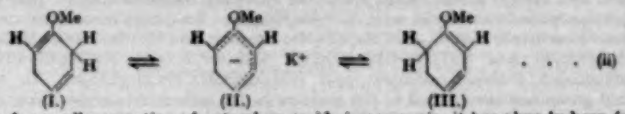
$$AH \underset{H^+}{\overset{NH_2^-}{\rightleftharpoons}} \underbrace{A^- B^-} \underset{NH_2^-}{\overset{H^+}{\rightleftharpoons}} BH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (i)$$

The equilibrium position is determined by the free-energy difference between the two possible conjugate acids AH and BH (Branch and Calvin, "The Theory of Organic Chemistry," N.Y., 1944, p. 289; de la Mare, Hughes, and Ingold, *J.*, 1948, 22). On the other hand, the products of irreversible proton addition are governed by the relative rates of combination of a proton with the various positions where a free charge appears in $\underbrace{A^- B^-}$. The expectation is that addition will be most rapid at the point of greatest free-charge density to give the strongest "acid" (*Faraday Soc. Discussion*, *loc. cit.*; Dewar, "The Electronic Theory of Organic Chemistry," Oxford, 1949, p. 103). This expectation is verified experimentally, the charge distribution being qualitatively estimated on the basis of the known electrical effects of substituents, and is confirmed by a study of the acidity of the conjugate acids AH and BH.

Apart from the evidence cited in the references above, the following observations lend further support to the theory. The enol of acetoacetic ester is formed when the sodium salt is treated with acid at a low temperature (Knorr, Rothe, and Averbeck, *Ber.*, 1911, **44**, 1138); the ionisation and the enolisation of ketones proceed at the same rate (Ives and Wilks, *J.*, 1938, 1455) as do their racemisation and deuterium exchange (Hsü, Ingold, and Wilson, *J.*, 1938, 78); $\beta\gamma$-unsaturated nitriles exchange the α-hydrogen for deuterium far more rapidly than they isomerise to the $\alpha\beta$-isomer (Ingold, de Salas, and Wilson, *J.*, 1936, 1328); and the metal salts formed from some $\alpha\beta$-unsaturated malonic esters on careful treatment with acid give the $\beta\gamma$-unsaturated esters (Hugh and Kon, *J.*, 1930, 775). It is apparent that the greatest free-charge density in the ions of hetero-enoid systems, *e.g.*, $\overbrace{C{=}C{-}C{=}C{-}O}$ is on the hetero-atom because of its greater electron-affinity compared with carbon. Accordingly, it might appear on this theory that irreversible addition of a proton should always occur in that position, as with acetoacetic ester. However, it is often difficult or impossible to find conditions where such combination is in fact irreversible for a proton, so attention can usually be confined to the less mobile carbon system. The hetero-atom in such cases acts as a charge-stabilising influence on the carbon system, the free-charge density being greatest on the carbon β to it.

Systems containing only carbon atoms have been little examined because the high energies of the anions result in very low acidities in the conjugate hydrocarbon "acids" (pK of the order 37—40; Morton, *Chem. Reviews*, 1944, **35**, 8). The products of reduction of substituted allyl alcohols, where such ions intervene, accord with the theory (Birch, *J.*, 1945, 809). By using stronger hydrocarbon "acids" such as dihydrobenzenes, it is possible to make the anions by the action of a metal amide in ammonia (pK about 34) (Part V, *loc. cit.*). The following

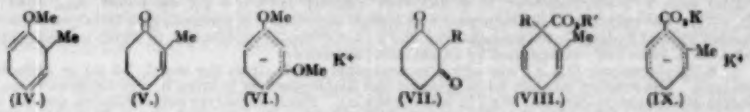
equilibrium which has now been examined is a direct illustration of equation (i) for a carbon system.†



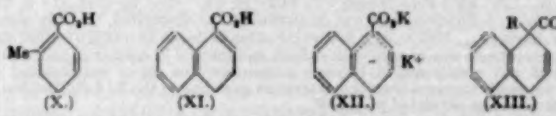
(I.) (II.) (III.) . . . (ii)

By the use of a small proportion of potassium amide in ammonia, it has already been found possible (Part V, *loc. cit.*) to convert the unconjugated 2 : 5-dihydroanisole (I) into the conjugated 2 : 3-dihydroanisole (III) of lower energy, the potassium salt (II) acting as a "turntable." The proton addition is *reversible*, because the ammonia and carbon "acids" of this type are comparable in strength. When several moles of potassium amide are used, the salt (II) is the major product and can be obtained either from (I) or from (III). If this salt is acted upon by an acid (ammonium chloride or water) strong compared with the carbon "acids," *irreversible* proton addition occurs and the product is chiefly the unconjugated (higher-energy) isomer (I). The absorption spectra and other properties make it quite clear that the conjugated (III) can thus be converted into the unconjugated (I).

The formation of the potassium salt (II) is attested by the deep red colour of the solution, and by the action of methyl iodide which causes addition of a methyl group in the same position as that taken up by the proton, since acid hydrolysis of the product (IV) gives 2-methyl*cyclo*hex-2-enone (V). Similarly, the potassium salt from 3-methyl-2 : 5-dihydroanisole gives rise, though in poor yield, to 2 : 3-dimethyl*cyclo*hex-2-enone. 1 : 3-Dimethoxy-2 : 5-dihydrobenzene gives a salt (VI) very readily, which is converted by the action of methyl iodide or 2-phenylethyl bromide, followed by acid hydrolysis, into 2-methyl*cyclo*hexane-1 : 3-dione (VII; R = Me) and 2-2′-*phenylethyl*cyclo*hexane*-1 : 3-*dione* (VII; R = CH_2·CH_2Ph), respectively.



(IV.) (V.) (VI.) (VII.) (VIII.) (IX.)



(X.) (XI.) (XII.) (XIII.)

The equilibrium (i) is also illustrated, though not quite so directly, by the reactions of several derivatives of 1 : 4-dihydrobenzoic acid. The reduction of *o*-toluic acid with sodium and ethanol in ammonia produces 2-*methyl*-1 : 4-*dihydrobenzoic acid* (VIII; R = R′ = H), which with potassium amide in ammonia forms a deep-red solution evidently containing the dipotassium salt (IX). The action of methyl iodide on the solution leads to 1 : 2-*dimethyl*-1 : 4-*dihydrobenzoic acid* (VIII; R = Me, R′ = H). The constitution of the last substance is proved by its lack of a light-absorption maximum in the region 2200—2800 A. (unconjugated double bonds) and by its oxidation by lead tetra-acetate to *o*-xylene. The action of ammonium chloride on the dipotassium salt (IX) is to add a proton to the 1-position, regenerating the original acid. However, if the acid is boiled with aqueous sodium hydroxide, an equilibrium is eventually established and the product isolated on acidification is a conjugated isomer ($\lambda_{max.}$ 2780 A.), probably 2-*methyl*-3 : 4-*dihydrobenzoic acid* (X).

An even more interesting case is that of 3 : 4-dihydro-1-naphthoic acid (XI). By the action of potassium amide in ammonia, this gives a dark red solution evidently containing the dipotassium salt (XII) because the action of methyl iodide leads to 1-*methyl*-1 : 4-*dihydro*-1-*naphthoic acid* (XIII; R = Me, R′ = H). The constitution of this compound is proved by its oxidation by lead tetra-acetate to 1-methylnaphthalene. The salt (XII) by the action of aqueous ammonium chloride gives rise, not to the starting acid, but to the unconjugated 1 : 4-dihydronaphthoic acid (XIII; R, R′ = H).

The observation that such dipotassium salts are formed quite readily led to an examination of the action of potassium amide in ammonia on several other unsaturated acids which should be

† Only the relevant hydrogen atoms are shown in these and subsequent formulæ.

capable of losing a proton from the unsaturated system. Exhaustive treatment with the reagent and methyl iodide brings about the following transformations: phenylacetic acid to 2-phenylpropane-2-carboxylic acid ($CPhMe_2{\cdot}CO_2H$); 1-naphthylacetic acid to *2-1'-naphthylpropane-2-carboxylic acid* ($C_{10}H_7{\cdot}CMe_2{\cdot}CO_2H$); crotonic acid ($CHMe{:}CH{\cdot}CO_2H$) to *2-methylbut-3-ene-2-carboxylic acid* ($CH_2{:}CH{\cdot}CMe_2{\cdot}CO_2H$); and sorbic acid ($CHMe{:}CH{\cdot}CH{:}CH{\cdot}CO_2H$) to *2-methylhexa-3 : 5-diene-2-carboxylic acid* ($CH_2{:}CH{\cdot}CH{:}CH{\cdot}CMe_2{\cdot}CO_2H$). In each case the methyl group has been added to the position in the mesomeric carbon-anion adjacent to the carboxyl group, where the charge density should be greatest. This happens even when, as in the last two examples, the double bonds are moved out of conjugation with the carboxyl by so doing.

It may also be noted that the irreversible addition of a proton, or of a methyl group, to the anion derived from the dihydroanisoles (*e.g.*, I), takes place in the 2-position, *ortho* to the methoxyl group and in the middle of the mesomeric system where the charge density should be greatest (cf. Dewar, *Faraday Soc. Discussion*, 1947, **2**, 261).

The foregoing experimental results thus make it plain that the intervention of mesomeric anions such as in (II) would explain the $\alpha\beta$-positions taken up by the hydrogen atoms in reductions by sodium and alcohols in liquid ammonia. Furthermore, reductions under conditions of reversible proton addition, which undoubtedly exist with calcium hexammoniate, would be expected to lead to the conjugated isomers of lower energy level, such as (II), and hence to further reduction. This agrees with the experimental findings (Part V, *loc. cit.*).

Experimental.

Interconversions of 2 : 5- and 2 : 3-Dihydroanisole.—2 : 5-Dihydroanisole (12 g.), b. p. 151°, n_D^{25} 1·4740 (obtained by the reduction of anisole), was added to potassium amide (from the metal, 0·5 g.) in ammonia (200 c.c.), and the dark red solution left for 20 minutes. It was then decomposed by adding ethanol (1 c.c.) drop by drop, with stirring, during 5 minutes, and then water (150 c.c.). Distillation of the oily product gave 2 : 3-dihydroanisole, b. p. 147—149° (mainly 148°) (8·5 g.), n_D^{25} 1·4630, $\lambda_{max.}$ 2680 A., $\varepsilon_{max.}^{mol.}$ 4270. The reduction of this substance with sodium and ethanol in ammonia gave tetrahydroanisole, detected by acid hydrolysis to *cyclo*hexanone, the 2 : 4-dinitrophenylhydrazone of which formed golden plates, m. p. 155—156°, undepressed by an authentic specimen.

2 : 3-Dihydroanisole (7·5 g.) was added to potassium amide (from the metal, 7·0 g.) in ammonia (200 c.c.). The solution was left for 10 minutes and decomposed by pouring it very cautiously into a solution of ammonium chloride (20 g.) in water (150 c.c.). Ether-extraction and distillation gave an oil (4·6 g.), b. p. 151—152°, n_D^{25} 1·4765 (Found: C, 76·5; H, 8·9. Calc. for $C_7H_{10}O$: C, 76·4; H, 9·1%). That this is chiefly 2 : 5-dihydroanisole was confirmed by the absorption, the only maximum between 2200 and 2800 A. having $\lambda_{max.}$ 2700 A., $\varepsilon_{max.}^{mol.}$ 580, which must be due to 10—15% of either starting material or anisole. The substance was treated with sodium and ethanol in ammonia, and, unlike the starting material, required only a little sodium before a momentary blue colour was obtained throughout the solution. The material recovered from this treatment gave rise to the 2 : 4-dinitrophenylhydrazone of *cyclo*hex-2-enone as orange-red plates, m. p. 165°.

Methylation of 2 : 5-Dihydroanisole.—2 : 5-Dihydroanisole (5 g.) and potassium amide (from the metal, 4 g.) in ammonia (100 c.c.) were left for 10 minutes, and methyl iodide was added drop by drop as rapidly as the rather violent reaction would allow until the red colour had disappeared. Water (50 c.c.) was then added and the oil collected with ether and refluxed with sulphuric acid (10%) for 15 minutes. The product was taken up in ether (15 c.c.) and shaken twice with water (20 c.c.) to remove most of the *cyclo*hexenone. The product was a colourless oil (1·4 g.), b. p. 169—174°, which gave rise to 2-methyl*cyclo*hexenone 2 : 4-dinitrophenylhydrazone as dark red prisms (from ethyl acetate), m. p. 204—205°, undepressed by an authentic specimen (Found: C, 54·2; H, 4·7. Calc. for $C_{15}H_{14}O_4N_4$: C, 53·8; H, 4·7%). The semicarbasone crystallised as cream-coloured prisms, m. p. 208°, from ethanol. 3-Methyl-2 : 5-dihydroanisole, treated similarly, gave a ketone, b. p. 85—90°/17 mm. The action on this of cold semicarbazide acetate in methanol for 10 minutes gave 3-methyl*cyclo*hex-2-enone semicarbazone, m. p. 199—200° (undepressed by an authentic specimen), which corresponds to unchanged starting material. The unreactive oil (0·4 g.), b. p. 93—95°/20 mm., was probably 2 : 3-dimethyl*cyclo*hex-2-enone (Found: C, 77·6; H, 9·5. Calc. for $C_8H_{12}O$: C, 77·4; H, 9·7%). The *2 : 4-dinitrophenylhydrazone* formed dark red needles (from ethyl acetate), m. p. 199—200° (Found: C, 55·5; H, 5·1. $C_{14}H_{16}O_4N_4$ requires C, 55·2; H, 5·2%); the semicarbazone formed colourless prisms, m. p. 227° (decomp.). Dupont (*Bull. Soc. chim. Belg.*, 1937, **46**, 21) gives m. p. 224° (slow heating) and 240° (fast heating).

Alkylation of 1 : 3-Dimethoxy-2 : 5-dihydrobenzene.—1 : 3-Dimethoxy-2 : 5-dihydrobenzene (7 g.) and potassium amide (from the metal, 2 g.) in ammonia (100 c.c.) were left for 10 minutes, and methyl iodide was added slowly with stirring to discharge the red colour. The oil obtained after addition of water (100 c.c.) and ether-extraction was heated on the steam-bath for 5 minutes with 2*N*-sulphuric acid (15 c.c.). The product was extracted with ether (3 × 25 c.c.) and the ethereal solution shaken with sodium hydroxide solution (5%) in small portions until acidification gave no more product. The crystalline solid so obtained crystallised from ethyl acetate as colourless prisms (2·8 g.), m. p. 206—207° (Found: C, 67·0; H, 7·8. Calc. for $C_7H_{10}O_2$: C, 66·7; H, 8·0%). The compound is certainly 2-methyl*cyclo*hexane-1 : 3-dione, m. p. 210° (Blaise and Maire, *Compt. rend.*, 1907, **144**, 573; *Bull. Soc. chim.*, 1908, **3**, 697), this being the only isomer which melts so high. Evaporation of the ether gave an alkali-insoluble oil (1·5 g.), b. p. 93—95°/12 mm.

The same reaction was carried out using 2-phenylethyl bromide (8 g.) instead of methyl iodide, the product being 2-2′-*phenylethylcyclohexane*-1 : 3-*dione*, crystallising from ethyl acetate as colourless prisms, m. p. 144—145° (Found : C, 77·7; H, 7·4. $C_{14}H_{16}O_2$ requires C, 77·8; H, 7·4%).

2-*Methyl*-1 : 4-*dihydrobenzoic Acid.*—*o*-Toluic acid (10 g.) in ammonia (300 c.c.) and ethanol (12 g.) was reduced by the action of sodium (5 g.). Ammonium sulphate (40 g.) was then added, followed by water (40 c.c.), and the ammonia evaporated off, finally under reduced pressure. Acidification of the residue gave an oil which rapidly solidified. This was taken up in ether (50 c.c.), dried (Na_2SO_4), the solvent removed, and light petroleum (b. p. 40—60°) (10 c.c.) added to the residue. The crystals (9·2 g.) were filtered off and recrystallised from a little light petroleum (b. p. 80—100°). 2-*Methyl*-1 : 4-*dihydrobenzoic acid* formed large colourless prisms (7·3 g.), m. p. 74—75° (Found : C, 69·5; H, 7·2. $C_8H_{10}O_2$ requires C, 69·6; H, 7·2%). Lack of conjugation of the double bonds was confirmed by the absence of a light-absorption maximum in the region 2200—2800 A. The action of potassium amide (3 mols.) in ammonia gave a dark red solution, but addition of ammonium sulphate and water as above led to recovery of the starting material.

2-*Methyl*-3 : 4(?)-*dihydrobenzoic Acid.*—The above acid (7 g.) was heated under reflux for 6 hours with sodium hydroxide solution (100 c.c.; 20%). Acidification gave an oil which solidified and crystallised from light petroleum (b. p. 80—100°) as colourless prisms (3·2 g.), m. p. 76—78°, considerably depressed by the starting material (Found : C, 69·6; H, 7·3. $C_8H_{10}O_2$ requires C, 69·6; H, 7·2%). Conjugation is shown by light absorption at $\lambda_{max.}$ 2780 A., $\varepsilon^{max.}_{max.}$ 3280 (ethanol). The *acid* is probably identical with that obtained, but not fully investigated by Hutchinson (*Ber.*, 1891, **24**, 178), but is not identical with 2-methyl-2 : 3-dihydrobenzoic acid, m. p. 128° (Perkin, *J.*, 1911, **99**, 758), or 2-methyl-4 : 5-dihydrobenzoic acid, m. p. 175° (Maxza and Carlò, *Gazzetta*, 1927, **57**, 315).

1 : 2-*Dimethyl*-1 : 4-*dihydrobenzoic Acid.*—2-Methyl-1 : 4-dihydrobenzoic acid (5 g.) was added to potassium amide (from the metal, 3 g.) in ammonia (100 c.c.), and methyl iodide (15 g.) in ether (20 c.c.) was cautiously added. Water (50 c.c.) was added, and the acid isolated by evaporation of the ammonia, acidification, and ether-extraction. Crystallisation from light petroleum (b. p. 40—60°) gave 1 : 2-*dimethyl*-1 : 4-*dihydrobenzoic acid* as large colourless prisms, (3·3 g.), m. p. 73—74°, considerably depressed on admixture with either of the preceding acids (Found : C, 70·8; H, 7·6. $C_9H_{12}O_2$ requires C, 71·0; H, 7·9%). Lack of conjugation is indicated by the absence of a light-absorption maximum between 2200 and 2800 A. The *ethyl ester* was a colourless oil, b. p. 105°/17 mm (Found : C, 73·4; H, 9·1. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·9%). The acid (3 g.) was added slowly to lead tetra-acetate (15 g.) and acetic acid (40 c.c.) at 50°. Rapid evolution of carbon dioxide took place with rise of temperature. Addition of water and extraction with a little ether gave an oil, b. p. 140—144° (1·4 g.), which, redistilled over sodium, had b. p. 143—144°, n_D^{18} 1·5030. *o*-Xylene has b. p. 144°, n_D^{20} 1·5046. Oxidation by refluxing nitric acid (25%) for 12 hours gave *o*-toluic acid, m. p. 103—104°, undepressed by an authentic specimen.

1 : 4-*Dihydronaphthoic Acid from* 3 : 4-*Dihydronaphthoic Acid.*—3 : 4-Dihydronaphthoic acid, m. p. 120° (2 g.), was added rapidly to potassium amide (from the metal, 5 g.) in ammonia (100 c.c.), and the dark red solution left for 3 minutes under an atmosphere of nitrogen. The solution was then forced by gas-pressure into a solution of ammonium chloride (25 g.) in water (75 c.c.), most of the ammonia removed under reduced pressure, and the solution acidified. The precipitated solid was dissolved in the minimum amount of dilute ammonia solution, and a concentrated solution of barium chloride added drop by drop until no further precipitate was formed. After filtration, the solution was acidified and the acid crystallised from light petroleum (b. p. 80—100°) with the aid of a little fuller's earth. It formed colourless, elongated prisms, m. p. 82—84°, undepressed by 1 : 4-dihydronaphthoic acid, m. p. 86—87°, but depressed by the starting material. Acidification of the barium salt which had been removed by filtration gave a solid, which was crystallised from acetic acid and identified as 1-naphthoic acid by its m. p. (162°, undepressed by an authentic specimen).

1-*Methyl*-1 : 4-*dihydro*-1-*naphthoic Acid.*—3 : 4-Dihydro-1-naphthoic acid (1·5 g.) was treated with potassium amide (from the metal, 0·8 g.) and methyl iodide to discharge the colour, and worked up as for the dihydrobenzoic acid above. The product was 1-*methyl*-1 : 4-*dihydro*-1-*naphthoic acid*, crystallising as small colourless prisms, m. p. 116—117°, from benzene–light petroleum (b. p. 40—60°) (Found : C, 78·9; H, 6·2. $C_{12}H_{12}O_2$ requires C, 78·6; H, 6·4%). On oxidation of the acid with lead tetra-acetate in acetic acid at 50°, carbon dioxide was evolved, and addition of water and ether-extraction gave an oil with an odour of naphthalene. This readily gave rise to 1-methylnaphthalene picrate as yellow needles (from ethanol), m. p. 154° (undepressed by an authentic specimen) (Found : C, 54·5; H, 3·6. Calc. for $C_{11}H_{10}O_7N_3$: C, 54·9; H, 3·5%).

2-*Phenylpropane*-2-*carboxylic Acid.*—Phenylacetic acid (10 g.) was added to potassium amide (from the metal, 10 g.) in ammonia (300 c.c.), followed by methyl iodide to discharge the red colour. The resultant acid was only partly crystalline, so the treatment was repeated. The product was then 2-phenylpropane-2-carboxylic acid, which crystallised from light petroleum (b. p. 80—100°) as large colourless elongated prisms, m. p. 80°, undepressed by an authentic specimen.

2-1′-*Naphthylpropane*-2-*carboxylic Acid.*—1-Naphthylacetic acid (5 g.) was treated twice, as above, using potassium amide (from the metal, 7 g.). The resulting 2-1′-*naphthylpropane*-2-*carboxylic acid* formed colourless prisms, m. p. 120—121°, from light petroleum (b. p. 60—80°) (Found : C, 78·6; H, 6·4. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·5%).

2-*Methylbut*-3-*ene*-2-*carboxylic Acid.*—Crotonic acid (5 g.), when added to a solution of potassium amide (from the metal, 7 g.) in ammonia (250 c.c.), gave a deep-red solution and a precipitate. Methyl iodide was added to discharge the colour, and the acid product isolated as above. Owing to the comparative insolubility of the potassium salt it was necessary to repeat the process twice more to obtain a uniform product, the salt in the last run being completely soluble. Distillation of the acid product gave two fractions : (*a*) (3·3 g.), b. p. 95—98°/15 mm., and (*b*) (0·6 g.), b. p. 110—117°/15 mm. Fraction (*a*) was 2-*methylbut*-3-*ene*-2-*carboxylic acid* (Found : C, 63·5; H, 9·0. $C_6H_{10}O_2$ requires C, 63·1; H, 8·8%). It gave an *amide* as colourless plates (from ethanol), m. p. 85° (Found : C, 63·7; H, 9·7. $C_6H_{11}ON$ requires C, 63·7; H, 9·7%). Hydrogenation (Pd–C) of the acid gave 1 : 1-dimethylbutyric acid, b. p.

183—185° [amide m. p. 102° (Found: C, 62·5; H, 11·1. Calc. for $C_8H_{15}ON$: C, 62·6; H, 11·3%)]. Haller and Bauer (*Compt. rend.*, 1909, **148**, 129) give m. p. 103—104° for the amide. From its analysis (Found: C, 64·7; H, 9·0. Calc. for $C_7H_{12}O_2$: C, 65·6; H, 9·4%) fraction (*b*) appears to be chiefly a trimethylcrotonic acid, probably 2-methylpent-3-ene-2-carboxylic acid.

2-*Methylhexa*-3 : 5-*diene*-2-*carboxylic Acid*.—Sorbic acid (10 g.) was treated three times as above, using potassium amide (from the metal, 7 g.) in ammonia (400 c.c.). The acid product was separated by distillation into two fractions: (*a*) (8 g.), b. p. 122—124°/13 mm., and (*b*) (0·7 g.), b. p. 130—134°/13 mm. Fraction (*a*) was 2-*methylhexa*-3 : 5-*diene*-2-*carboxylic acid* (Found: C, 68·7; H, 8·6. $C_7H_{10}O_2$ requires C, 68·6; H, 8·6%). It gave rise to the *amide* as colourless plates (from ethanol), m. p. 82° (Found: C, 69·5; H, 9·2. $C_7H_{11}ON$ requires C, 69·0; H, 9·3%). On hydrogenation (Pd–C) the acid absorbed 2 moles of hydrogen, the first much more readily than the second, to give 2 : 2-dimethylhexanoic acid, b. p. 123°/16 mm. (Found: C, 66·5; H, 11·0. Calc. for $C_8H_{16}O_2$: C, 66·7; H, 11·1%). The amide crystallised as colourless plates (from ethanol), m. p. 92° (Found: C, 66·7; H, 11·6. Calc. for $C_8H_{17}ON$: C, 67·1; H, 11·9%). Its m. p. was not depressed by an authentic specimen, m. p. 92°, prepared by the method of Locquin and Leers (*Compt. rend.*, 1924, **178**, 2095). The diene-acid, after several months in a sealed tube, had polymerised to a colourless glass, soluble in acetone or aqueous sodium hydroxide.

Absorption spectra are by Dr. F. B. Strauss.

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322. *The Nitration of Dimethylaniline to Tetryl, 2 : 4 : 6 : N-Tetranitromethylaniline. The Course of the Reaction.*

By C. E. CLARKSON, I. G. HOLDEN, and T. MALKIN.

The formation of tetryl from dimethylaniline proceeds in two main stages: (1) dimethylaniline ⟶ 2 : 4-dinitrodimethylaniline, (2) 2 : 4-dinitrodimethylaniline ⟶ tetryl, the latter stage proceeding largely *via* 2 : 4-dinitromononethylaniline, but also *via* dimethylpicramide.

Stage (1) is catalysed by nitrous acid, probably owing to the production of nitronium ions from dinitrogen tetroxide, $N_2O_4 \rightleftharpoons NO_2^+ + NO_3^-$ (*cf.* Addison and Thompson, *J.*, 1949, S 211; Levy and Scaife, *J.*, 1946, 1093).

Stage (2) is accelerated in a different manner by nitrous acid, which is found to be a powerful demethylating agent. The mechanism of the transformation 2 : 4-dinitrophenylnitramine ⟶ methylpicramide is discussed.

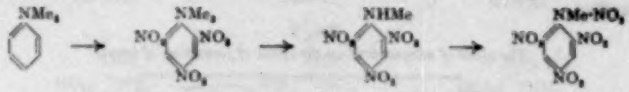
TETRYL was first prepared by Mertens (*Ber.*, 1877, **10**, 995) as yellow crystals, m. p. 127°, by boiling dimethylaniline with fuming nitric acid, but he was unable to obtain satisfactory analytical results, presumably because of the explosive properties. A little later its constitution was established by van Romburgh (*Rec. Trav. chim.*, 1883, **2**, 103; 1889, **8**, 215) who found that tetryl could be prepared by the nitration of both methyl- and dimethyl-aniline, and, from the fact that carbon dioxide and oxides of nitrogen were evolved profusely in the latter case, but not appreciably in the former, he concluded that tetryl contained only one methyl group; this he confirmed by preparing tetryl from *N*-methyl- and *NN*-dimethyl-picramide, and by synthesis from picryl chloride and potassium methylnitramine.

Tetryl has long been used both as a high explosive and as an initiator or primer for high explosives and propellants, and there is much information on its preparation [Langscheidt, *Z. ges. Schiess. u. Sprengstoffw.*, 1912, **7**, 445; van Duin, *Rec. Trav. chim.*, 1917, **37**, 111; Wride, *Arms and Explosives*, 1923, **28**, 6; Tanner, *Chem. Met. Eng.*, 1923, **29**, 404; Desvergnes, *Mem. Poudres*, 1922, **19**, 217; Bain, *Army Ordnance*, 1926, **6**, 435; Attillio Izzio, (*Review*) *Industria chimica*, 1933, **8**, 171; Chao Lung Tseng and Tu Chi Lin, *J. Chem. Eng. China*, 1933, **2**, 128; Desvergnes, *Chim. et Ind.*, 1930, **24**, 785; Nolan and Clapham, *Sci. Proc. Roy. Dublin Soc.*, 1923, **17**, 219).

The only practicable method of preparation is the nitration of dimethylaniline, and most of those studied by the observers noted above involve the addition of a solution of dimethylaniline in concentrated sulphuric acid (referred to subsequently as D.M.A.S.) to nitric acid, or to a mixture of nitric and sulphuric acids, under a variety of conditions of concentration and temperature. The nitration of methylaniline, which would appear to be a more direct route, gives a much lower yield (75% compared with 93%), owing mainly to *meta*-nitration, leading to 2 : 3 : 4 : 6 : *N*-pentanitromethylaniline or " meta-tetryl " (cf. Knowles, *Ind. Eng. Chem.*, 1920,

12, 246; Forster and Coulson, *J.*, 1922, **121**, 1988), a particularly undesirable impurity which catalyses the decomposition of tetryl (Hinshelwood, *J.*, 1921, **119**, 721).

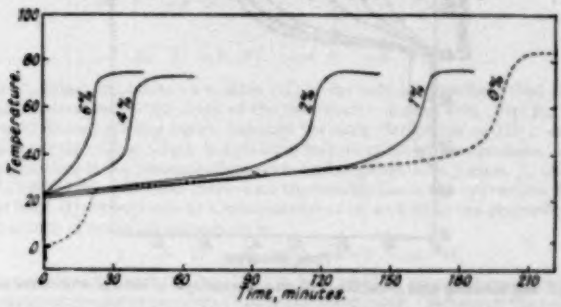
Of the methods referred to above, that of Wride is of interest in that he recognised two main stages in the reaction. In the first stage he added D.M.A.S. to a nitrating mixture of nitric and sulphuric acids, keeping the temperature at 45°, and in the second, he warmed the solution to 65° and maintained it at this temperature until the reaction was complete. Wride considered that stage I was conversion into dimethylpicramide, and that stage II was oxidation and nitration of this to tetryl, *viz.* :



In this view, generally accepted hitherto, Wride was, however, only partly correct, for on plotting a time–temperature curve of the reaction after mixing D.M.A.S. with nitrating acid in a Dewar vessel (Fig. 1, for which we are indebted to Drs. H. D. Springall and T. H. Bevan) it is seen, in agreement with Wride, that there are two main stages, but on drowning the reaction mixture with water, after the completion of the first stage, one obtains an almost quantitative yield of 2 : 4-dinitrodimethylaniline.

Fig. 1.

The effect of nitrous acid on the speed of formation of tetryl.



D.M.A.S. and nitrating acid containing the above percentages of nitrous acid mixed at −7°.

Time–temperature curves taken as indicated above show that the presence of nitrous acid increases the rate of both stages of the reaction (Figs. 1 and 2; Drs. Springall and Bevan, unpublished). The type of effect seems to be different in the two stages, since very small amounts affect stage I; for example, any amount above 0·3% in the nitrating acid makes stage I practically instantaneous, whereas increasing amounts up to 6% still further increase the rate of stage II. One gains the impression that in stage I the action is catalytic, whilst in stage II nitrous acid is a reactant rather than a catalyst.

Before dealing with these stages in detail, it will assist later discussion if the main facts of a tetryl preparation are described. D.M.A.S. is added with vigorous stirring to nitrating acid in a flask surrounded by ice, and the temperature is not allowed to exceed 30—35°. The first drop of D.M.A.S. produces a deep red colour which is intensified as the addition proceeds. After the addition, the reaction flask is surrounded by a water-bath at 90—100°, which is removed when the contents of the flask reach 60°, from which point the temperature rises at a convenient rate without external heat. During this rise, the reddish-orange solution becomes darker and less clear, and at a little above 70° assumes a purplish colour. At this stage, tetryl begins to separate as an oil, and soon solidifies in a fine crystalline form, the separation being accompanied by a violent evolution of brown fumes (fume-off) and a rapid rise in temperature, which should not be allowed to exceed 100° (ice-bath).

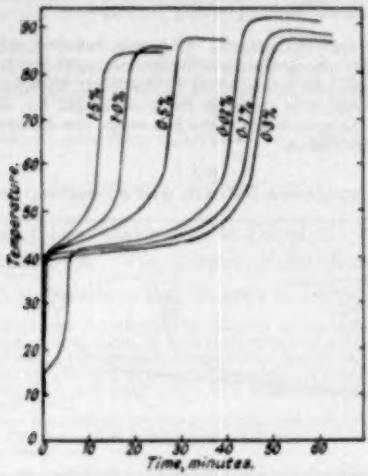
Stage I. Dimethylaniline ⟶ 2 : 4-*Dinitrodimethylaniline*.—Dinitration is rapid and it is difficult to isolate the mononitro-compound. If, however, the reaction is carried out at −20°

and the reactants are poured into cold alkali, it is possible to isolate a small amount of *p*-nitrodimethylaniline (unpublished work by Dr. T. H. Bevan).

The main point of interest in this stage is the action of traces of nitrous acid, which appears to be catalytic. Martinsen (*Z. physikal. Chem.*, 1904, **50**, 385; see also Benford and Ingold, *J.*, 1939, 931, for fuller references) has observed a similar effect in the nitration of phenol, and he considers, but rejects, the view that rapid nitrosation, followed by oxidation, is the explanation. Unpublished work by Dr. H. D. Springall has shown that this view cannot be supported in the present case, since *p*-nitrosodimethylaniline gives a much lower yield of tetryl than does dimethylaniline.

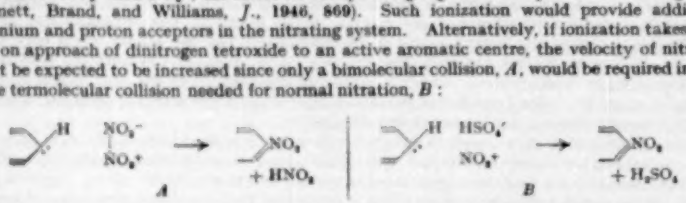
FIG. 2.

The effect of nitrous acid on the speed of formation of tetryl.



D.M.A.S. and nitrating acid containing the above percentages of nitrous acid mixed at 10°.

The catalytic action may be due to ionization or even potential ionization of dinitrogen tetroxide to NO_3^- and NO_2^+, the latter nowadays being regarded as a powerful nitrating agent (Bennett, Brand, and Williams, *J.*, 1946, 869). Such ionization would provide additional nitronium and proton acceptors in the nitrating system. Alternatively, if ionization takes place only on approach of dinitrogen tetroxide to an active aromatic centre, the velocity of nitration might be expected to be increased since only a bimolecular collision, *A*, would be required instead of the termolecular collision needed for normal nitration, *B*:



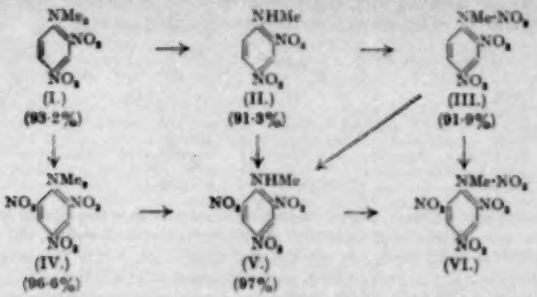
The important point is that the concentration of nitrous acid is not reduced by this process:

$$2HNO_2 \longrightarrow N_2O_3 \longrightarrow NO + NO_2 \xrightarrow{HNO_3} N_2O_4 \longrightarrow NO_3^- + NO_2^+$$

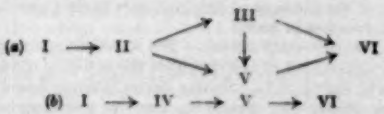
Thus for each molecule nitrated, one molecule of nitrous ion is produced, and one molecule of nitric acid is reduced to nitrous acid.

Stage II. 2:4-*Dinitrodimethylaniline* ⟶ *Tetryl.*—When at this stage the mixture was poured into water at different intervals, the only intermediate isolated was 2:4-dinitromonomethylaniline, and therefore the course of the reaction must be arrived at indirectly. Possible routes

are given in the following scheme, and from a consideration of the observed yield of tetryl from each intermediate, given in parentheses, it is possible to deduce the main course of the reaction.



Thus, a 93·2% yield of tetryl from (I) can be obtained either by a combination of routes (*a*) and (*b*), or by route (*b*) exclusively, assuming a loss in yield in stage I ⟶ IV :



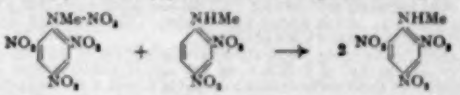
The evidence is against the latter view, since (II) is the only intermediate that can be isolated. Moreover, the acceleration of this stage of the reaction by nitrous acid (Fig. 2), which is found to be a powerful demethylating agent, suggests the early formation of (II); and, finally, the production of a purple colour, which is a striking feature of tetryl preparations, is a well-known property of nitramines in the presence of concentrated sulphuric acid (Orton, *J.*, 1902, **806**; Orton and Smith, *J.*, 1905, **389**). If, then, there is no appreciable loss in the conversion (I ⟶ IV), the yield of tetryl from (I) corresponds to a combination of (*a*) and (*b*) in the proportion of 1·8 to 1·0.

The main course of route (*a*) appears to be

$$\text{I} \longrightarrow \text{II} \longrightarrow \text{III} \longrightarrow \text{V} \longrightarrow \text{VI},$$

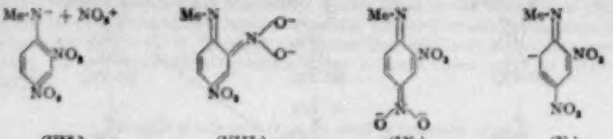
for we find it possible to convert (II) into (III) in 94% yield by means of concentrated nitric acid (70%), whereas all attempts to prepare (V) from (II) have failed. Moreover, the conversion of (II) into tetryl is always accompanied by the characteristic violet colour. This we consider is an indication of the intra(? inter)-molecular change (III ⟶ V). Aromatic nitramines are known to undergo intramolecular changes readily in the presence of sulphuric acid (Bamberger, *Ber.*, 1897, **30**, 1253; Orton and Smith, *loc. cit.*), and, in agreement with this, (III) can be converted by means of sulphuric acid into (V) in 90% yield. Moreover, (III) is always converted into tetryl more readily by a mixture of nitric and sulphuric acids than by nitric acid alone.

Arising out of the reactions in route (*a*) are the interesting points concerning the nature of the purple colour, and the mechanism of the change (III ⟶ V). On the latter question, our results lead us to somewhat the same conclusions as those of Bradfield and Orton (*J.*, 1929, 917), who studied the transformations of simple aromatic nitramines and considered their evidence to be in harmony with an intramolecular process, although they also obtained evidence of extranuclear migration of nitro-groups. We, too, find evidence for the latter. Thus, equimolecular amounts of tetryl and 2 : 4-dinitromonomethylaniline, when kept overnight in concentrated sulphuric acid, yield methylpicramide almost quantitatively :



No extranuclear migration takes place, however, when 2 : 4-dinitrophenylmethylnitramine and *p*-nitromonomethylaniline or 2 : 4-dinitrodimethylaniline are similarly treated, the nitramine merely changing into methylpicramide.

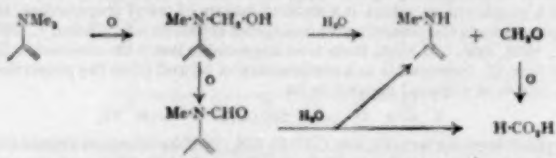
These results, in conjunction with the production of the purple colour, suggest the possibility of an ionic mechanism. Dinitrophenylmethylnitramine, in a medium of high dielectric constant, for example, nitrating acid, might ionize to (VII), which could exist in the canonical forms (VIII, IX, and X), which would be expected to be highly coloured:



(VII.) (VIII.) (IX.) (X.)

This ionization produces a planar, highly resonating system, with a consequent gain in stability, and therefore has some degree of probability. In the presence of nitronium, (X) will be nitrated in the *ortho*-position to yield the highly symmetrical trinitro-ion, but at this stage the solubility factor comes into play and this ion combines with nitronium to form tetryl, which is precipitated. An ionic mechanism of this kind, which implies an almost instantaneous reaction from dinitromonomethylaniline, would explain the difficulty of isolating any other intermediate. On the above view, the distinction between an inter- and an intra-molecular reaction is extremely fine, and whilst a nitronium ion at the moment of dissociation is likely to be the nearest to the vacant *ortho*-position it would not necessarily be so.

Demethylation of 2 : 4-*Dinitrodimethylanilins.*—The accelerating effect of nitrous acid in the second stage of the tetryl reactions led us to investigate the action of nitrous acid on 2 : 4-dinitromethylaniline, and we found that it is an effective demethylating agent, converting the latter, in 65% sulphuric acid, rapidly in the cold, into 2 : 4-dinitrophenylmethylnitrosamine. Comparative tests show that nitrous acid is a much more rapid demethylating agent than nitric acid. Both formaldehyde and formic acid have been identified as products of demethylation, which appears to proceed through the following stages:



We have no evidence that would indicate the presence of methyl alcohol at any stage of the demethylation, and we have not observed even traces of esters of nitric or nitrous acid.

Formic acid can be isolated from the tetryl reaction in large amounts, if the temperature is not allowed to exceed 60°, and its decomposition by nitrating acid at higher temperatures is the main cause of the characteristic "fume-off."

Experimental.

Preparation of Tetryl.—Our work was primarily undertaken to determine the optimum conditions for the continuous production of tetryl in high yield and quality, the latter being of great importance for service material, which has to pass stringent tests for stability (cf. Farmer, *J.*, 1920, 1433, 1602). The following concentrations of D.M.A.S. and nitrating acid were found suitable. Concentration of the two acids were variable over a small range, but the water content, calculated on the mixed D.M.A.S. and nitrating acid, should not vary by more than ±2%.

Preparation of D.M.A.S. Dimethylaniline (60 c.c.) was run into 96% sulphuric acid (180 c.c.) with vigorous stirring and ice-cooling, the temperature being kept below 30° (local heating can give rise to tetramethylbenzidine; the acid concentration is not significant, but was used for technical reasons).

Nitrating acid. 99% Sulphuric acid (360 c.c.; *d* 1·84) was added to ice (250 g.), with external cooling, and 98% nitric acid (227 c.c.; *d* 1·5) added with stirring. Nitrating acid made with ordinary 70% nitric acid always gave a slightly lower yield of tetryl.

Nitration. The main details of the preparation have been given in the Introduction. A convenient laboratory scale is to add 60 c.c. of D.M.A.S. to 240 c.c. of nitrating acid in a 1-l. round-bottom "Quickfit" flask, fitted with three necks to take a dropping funnel, a thermometer, and a stirrer. After the addition of D.M.A.S., the dropping funnel is replaced by a wide reflux-tube to take off the fumes, and the experiment should be carried out only in a most efficient fume chamber.

After the "fume-off" already described, and when it is clear that the temperature of the reaction is falling, the reaction vessel is heated in a water-bath for half an hour to clarify the solution and expel

oxides of nitrogen. After cooling to room temperature the tetryl is filtered off through a sintered-glass funnel and well washed with water.

"*Steam blowing.*" The simplest way of purifying tetryl is to suspend it in 500 c.c. of water in a 1½-l. flask and pass steam through it for half an hour. This removes surface and occluded acid, and converts any "meta-tetryl" and other impurities into the water-soluble "meta-hydroxytetryl" (3-hydroxy-2 : 4 : 6 : *N*-tetranitromethylaniline) and picric acid, respectively. After cooling, tetryl is filtered off, washed with water, and dried in the air on filter-paper trays. In a good experiment the wash-water should be just faintly yellow. Yield, 92—93%; m. p. 126·5—129°. Tetryl crystallises from alcohol and aqueous acetone.

2 : 4-*Dinitrodimethylaniline*.—The above D.M.A.S. (60 c.c.) was slowly added with stirring to nitrating acid (240 c.c.), the temperature being kept below 30°. After 5 minutes, the dark red solution was poured into water (2·5 l.) with stirring, and the orange-yellow granular precipitate filtered off, dried, and crystallised from alcohol containing a little acetone. The yield was practically quantitative. 2 : 4-Dinitrodimethylaniline crystallises in two forms: fine needles, m. p. 77°, and truncated octahedra, m. p. 87°.

This experiment is merely the first stage of a tetryl preparation, and the quantitative yield of dinitro-compound is confirmed by the fact that both the latter and dimethylaniline give the same final yield of tetryl. The above preparation uses a large excess of nitrating acid, and twice the amount of D.M.A.S. can be used if the reaction is to be used as a preparation of the dinitro-compound.

Action of Nitrous Acid on 2 : 4-*Dinitrodimethylaniline*.—2 : 4-Dinitrodimethylaniline (2 g.) was dissolved in 85% sulphuric acid (20 c.c.) with gentle warming, and to the cold solution sodium nitrite (3 g.) was added in small quantities with stirring and cooling. A light-yellow precipitate quickly formed, and was filtered off, washed, and dried (1·8 g.; m. p. 83°). Crystallised from alcohol, it separated in yellow hexagonal plates, m. p. 85°, giving no depression with an authentic specimen of 2 : 4-dinitro-*N*-nitrosomonomethylaniline. If the temperature is allowed to rise, 2 : 4-dinitromonomethylaniline is the main product.

Isolation of Formic Acid from a Tetryl Preparation.—In order to facilitate isolation of the formic acid, conditions were chosen to give a large excess of D.M.A.S. and so reduce to a minimum the amount of nitrous and nitric acids present. D.M.A.S. (60 c.c.) was slowly added with stirring and cooling to standard nitrating acid (76 c.c.; 240 c.c. required for a normal tetryl preparation), and the temperature was not allowed to rise above 45°. After several hours at this temperature, tetryl began to separate. After being kept overnight, this was filtered off, and the filtrate was diluted with 4—5 times its bulk of water and filtered from a reddish tarry precipitate. After treatment with ferrous sulphate solution and filtration, the liquid was steam-distilled. *ca.* 2 l. of distillate were neutralised with aqueous sodium hydroxide and evaporated to dryness, to yield 2 g. of sodium formate, which responded to all the usual tests, including conversion into oxalate. This yield is $\simeq$ 80%, calculated on the amount of tetryl formed.

Preparation of 2 : 4-*Dinitromonomethylaniline* (private communication from Dr. J. K. N. Jones).—2 : 4-Dinitrodimethylaniline (20 g.) was refluxed with dilute nitric acid (19 c.c. of HNO_3, *d* 1·42, in 200 c.c. of water) until the heavy oily layer changed to the solid dinitromonomethylaniline (about 1 hour). The reaction mixture was then cooled and filtered; the product, crystallised from acetone, had m. p. 178° (yield, practically quantitative).

When a current of air was passed through the reaction mixture, formaldehyde was detected, by smell and by formation of the 2 : 4-dinitrophenylhydrazone (Dr. Jones informs us that the corresponding diethyl derivative behaves similarly, yielding acetaldehyde).

2 : 4-*Dinitrophenylmethylnitramine*.—2 : 4-Dinitromonomethylaniline (5 g.) was added to 70% nitric acid (100 c.c.; *d* 1·42) and gently warmed to about 40° to complete dissolution. After storage in water at room temperature for 2½ hours, the solution was poured into 800 c.c. of water, a light yellow granular precipitate separating. This was filtered off, washed, and dried (5·1 g.), having m. p. 111°, raised to 115° by crystallisation from alcohol. The *nitramine* crystallised in light yellow hexagonal prisms (Found: C, 34·3, 34·4; H, 2·63, 2·66; N, 22·0, 21·7. $C_7H_5O_8N_5$ requires C, 34·7; H, 2·5; N, 23·1%).

The structure was confirmed by removal of the *N*-nitro-group by heating the substance with phenol to yield 2 : 4-dinitromonomethylaniline (cf. Mertens, *Ber.*, 1896, **19**, 2123, and Romburgh, *Rec. Trav. chim.*, 1896, **5**, 240).

This nitramine and the isomeric methylpicramide have the same m. p., which may explain why the former has not previously been described. We consider it probable that the product obtained by Hodgson and Turner (*J.*, 1942, 584) by the action of 70% nitric acid on dimethylaniline, and thought to be methylpicramide, was actually 2 : 4-dinitrophenylmethylnitramine.

Conversion of 2 : 4-*Dinitrophenylmethylnitramine into Methylpicramide*.—The nitramine (0·2 g.) was dissolved in concentrated sulphuric acid (2 c.c.), and the solution was diluted with water (1·5 c.c.). Some material was first precipitated but dissolved again as the temperature rose. After a few minutes the solution was diluted with water; the resulting precipitate, filtered off and dried (yield, 0·18 g.), had m. p. 111—112° (mixed m. p. with original nitramine, 85°; mixed m. p. with methylpicramide, 113—114°).

Yield of Tetryl from Possible Intermediates.—(1) *From* 2 : 4-*dinitrodimethylaniline*. The dinitro-compound (5 g.) was dissolved in 75% sulphuric acid (50 c.c.), and 98% nitric acid (11 c.c.) was added with stirring, the temperature being kept below 40°. Sodium nitrite (0·05 g.) was then added, and the reaction was then continued as described for the standard tetryl preparation. The product was steam-blown and dried. The yield was 6·4 g. (93·2%).

(2) *From* 2 : 4-*dinitromonomethylaniline*. The dinitro-compound (5 g.) was treated as in (1). There was no appreciable "fume-off." The yield was 6·65 g. (91·3%).

(3) *From* 2 : 4-*dinitrophenylmethylnitramine*. 2 G. of this substance were heated with 24 c.c. of nitrating acid of composition H_2SO_4 64, HNO_3 15, H_2O 21%, and the nitration completed as in (1), the yield being 2·18 g. (91·9%).

(4) *From monomethylpicramide*. 1 G. of this material was nitrated under the same conditions as in (3), *i.e.*, 12 c.c. of nitrating acid of the same strength. The yield was 1·15 g. (97%).

(5) *From dimethylpicramide*. 2 G. of the substance, nitrated as in (3), gave 2·165 g. (96·6%).

Inter- and Intra-molecular Changes.—(*a*) Tetryl (1·46 g.) in cold concentrated sulphuric acid (10 c.c.)

was added to 2 : 4-dinitromonomethylaniline (1 g.) in the same solvent (10 c.c.) (equimolecular proportions of reactants). After being kept overnight, the solution was poured into water, and the light-orange precipitate filtered off. Examination under the polarising microscope showed it to be methylpicramide, with no indication of unchanged material. After one crystallisation from alcohol it had m. p. and mixed m. p. 115°.

(*b*) 2 : 4-Dinitrophenylmethylnitramine (0·57 g.) and 2 : 4-dinitrodimethylaniline (0·5 g.) were each dissolved in 10 c.c. of concentrated sulphuric acid, and the solutions mixed. After being kept overnight, the solution was poured into water, and the yellow precipitate filtered off. Microscopic examination, confirmed by fractional crystallisation from alcohol, showed the products to be methylpicramide and 2 : 4-dinitrodimethylaniline.

(*c*) A similar experiment, using *p*-nitromethylaniline and 2 : 4-dinitrophenylnitramine, yielded unchanged *p*-nitromethylaniline and methylpicramide.

Development of Purple Colour by Possible Tetryl Intermediates.—A small amount of substance was warmed on the water-bath with standard nitrating acid. 2 : 4-Dinitrodimethylaniline, 2 : 4-dinitromonomethylaniline, 2 : 4-dinitro-*N*-nitrosomonomethylaniline, and 2 : 4-dinitrophenylmethylnitramine gave a purple colour, but mono- and di-methylpicramide did not.

This work was carried out under the direction of Professors W. E. Garner, F.R.S., and E. L. Hirst, F.R.S., and is published by permission of the Chief Scientist, Ministry of Supply. We are grateful to Dr. A. Forster for placing his wide experience in tetryl manufacture at our disposal, and to Drs. H. D. Springall, J. K. N. Jones, and T. H. Bevan for permission to use certain of their results. Our best thanks are due to all the above-named and to Drs. W. J. Dunning and J. F. W. McOmie for helpful discussion.

THE UNIVERSITY, BRISTOL, 8. [*Received, March* 2*nd*, 1950.]

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323. *The* Euphorbia *Resins. Part IV. A Comparative Study of Euphol and Tirucallol.*

By DENNIS W. HAINES and FRANK L. WARREN.

It is shown that in tirucallol the hydroxy-group is secondary and the *iso*propylidene group is not attached directly to a ring.

Euphenyl and tirucallenyl acetates are oxidised by chromic acid to diketoeuphenyl acetate and *diketotirucallenyl acetate* which contain the grouping —CO—C(=)—C(=)—CO— and are reduced to *diketoeuphanyl* and *diketotirucallanyl acetates*, respectively.

Euphol and tirucallol are thus isomeric tetracyclic triterpenes, $C_{30}H_{50}O$, containing the groupings >CH·OH, —CH=CMe$_2$ and —CH$_2$—C(=)—C(=)—CH$_2$—. Tirucallenol is converted into *diketotirucallane* which is different from *diketoeuphane*.

BOTH euphol (euphadienol) (cf. Newbold and Spring, *J.*, 1944, **249**; Jeger and Krusi, *Helv. Chim. Acta*, 1947, **30**, 2045; McDonald, Warren, and Williams, *J.*, 1949, 155) and tirucallol (tirucalladienol) (cf. Haines and Warren, *J.*, 1949, 2554) have been shown to be tetracyclic triterpene alcohols, $C_{30}H_{50}O$, containing an *iso*propylidene group and an inert double bond. We have now shown that tirucallol, like euphol, contains a secondary hydroxyl group since dehydrogenation of tirucallol and tirucallenol gives tirucalladienone (*oxime*, $C_{30}H_{49}ON$, m. p. 218—220°) and *tirucallenone*, $C_{30}H_{48}O$, m. p. 62—64° (*oxime*, m. p. 236·5—237·5°; *semicarbazone*, m. p. 214—215°) respectively. These two ketones from tirucallol are different from the corresponding ketones prepared previously by Bennett and Warren (*J.*, 1950, 697) from euphol.

To obtain further information on the mode of linkage of the *iso*propylidene group, *tirucallyl acetate dibromide*, $C_{32}H_{52}O_2Br_2$, was boiled with alcoholic potash: *monobromotirucallol*, $C_{30}H_{49}OBr$, further characterised as its *acetate*, $C_{32}H_{51}O_2Br$, was obtained. This behaviour is similar to that found for euphyl acetate dibromide by McDonald *et al.* (*loc. cit.*) so that the *iso*propylidene group is similarly joined in euphol and tirucallol and is probably not attached directly to a ring.

In a previous communication it was shown that euphenyl acetate was readily oxidised to mono- and di-ketoeuphenyl acetate, in which respect it paralleled the behaviour of cryptosterol, lanosterol, and elemolic acid. This oxidation has been repeated with larger quantities to study further the nature of the inert ethylenic linkage. Diketoeuphenyl acetate has now been obtained melting at 106—107° [previously reported by McDonald *et al.* (*loc. cit.*) as melting at 97°] and is hydrolysed to *diketoeuphenol*, $C_{30}H_{44}O_3$. *Diketoeuphenone*, $C_{28}H_{44}O_3$, was obtained by direct oxidation of euphenol with chromic acid.

The light-extinction curve for monoketoeuphenyl acetate in hexane showed a pronounced maximum at λ 246 mμ. (log $\varepsilon_{max.}$ 4·05) which, corrected for alcohol as solvent, gives $\lambda^{alc.}_{max.}$ 253 mμ. (Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123) and is indicative of an αββ-trisubstituted αβ-unsaturated ketone, as was found by Dorée, McGhie, and Kurzer (*J.*, 1948, 988) for

ketolanostenyl acetate. Furthermore, diketoeuphenyl acetate showed a pronounced shift in the absorption maximum towards the red similar to that found previously for diketolanostenyl acetate for which the chromophoric grouping —CO—C(=)—C(=)—CO—, formed from —CH_2—C(=)—C(=)—CH_2—, has been suggested by Dorée *et al.* (*loc. cit.*).

The 1 : 4-arrangement of the keto-groups in diketoeuphenyl acetate is probably such that the two polar groups act in opposite directions, for then the polarity would be pronouncedly less than that of the monoketoeuphenyl acetate which is more strongly adsorbed on a column of alumina than is the diketo-compound. Furthermore, diketoeuphenyl acetate failed in our hands to give a pyridazine when heated with hydrazine.

The chromic acid oxidation of tirucallenyl acetate gave a difficultly separable mixture of mono- and di-keto-compounds, but prolonged oxidation gave pure *diketotirucallenyl acetate*, $C_{32}H_{48}O_4$, readily hydrolysed to *diketotirucallenol*, $C_{30}H_{46}O_3$. The extinction curve of diketotirucallenyl acetate shows a maximum similar to those found for the corresponding compounds from euphol and lanosterol, and the chromophoric grouping is certainly similar.

	Monoketone.		Diketone.	
	$\lambda^{alc.}_{max.}$, mμ.	log $\epsilon_{max.}$	$\lambda^{alc.}_{max.}$, mμ.	log $\epsilon_{max.}$
Euphenyl acetate	253	4·05	275	3·94
Tirucallenyl acetate	—	—	274	3·98
Lanostenyl acetate	255	4·08	275	3·94

Thus both euphol and tirucallol possess a secondary hydroxyl and the groupings —CH=CMe$_2$ and —CH_2—C(=)—C(=)—CH_2—. In order to find whether the hydrocarbon skeletons were the same, attempts were made to dehydrate euphol with phosphorus oxychloride and pentachloride, but only oily products were obtained. Attempts to prepare the hydrocarbon by the Wolff–Kishner reduction of tirucallenone semicarbazone, as well as by the modified Clemmensen reduction of the ketone (cf. Dorée, McGhie, and Kurzer, *J.*, 1947, 1468), gave only oily products. The appreciable increase in melting point recorded by Dorée, McGhie, and Kurzer (1948, *loc. cit.*) on reducing diketolanostenyl acetate to diketolanostanyl acetate led us to attempt to reduce the inert double bond in euphol and tirucallol in a similar way, with a view to obtaining later crystalline derivatives of the fully saturated deoxy-compounds. The yellow diketoeuphenyl acetate was hydrogenated smoothly with Adams's catalyst and hydrogen to give colourless *diketoeuphanyl acetate*, $C_{32}H_{52}O_4$; but, when reduction was attempted with zinc in either hot or cold acetic acid, colourless compounds were obtained which appeared from analyses to be impure. Furthermore, diketoeuphanyl acetate on hydrolysis failed to give a crystalline alcohol. The hydrolysis product, however, on oxidation with chromic acid gave *diketoeuphanone*, $C_{30}H_{48}O_3$, also obtained by the catalytic reduction of diketoeuphenone.

Diketotirucallenyl acetate was readily hydrogenated either catalytically or with zinc and acetic acid, to give colourless *diketotirucallanyl acetate*, $C_{32}H_{52}O_4$, which was hydrolysed to *diketotirucallanol*, $C_{30}H_{50}O_3$, which in turn gave *diketotirucallanone*, $C_{30}H_{48}O_3$. The physical constants for these compounds, compared with those for lanosterol, are shown in the table.

	Diketodihydro-compound,		Diketotetrahydro-compound,	
	m. p.	$[\alpha]_D$.	m. p.	$[\alpha]_D$.
Euphyl acetate	106—107°	+25·7°	190—191·5°	−15·2°
Euphol	115—116	+32·1	—	—
Euphone	63—64	+31·1	186—187	−144·7
Tirucallyl acetate	135—136	−17·1	222—224	−131
Tirucallol	136—137	−24·5	199—200	−144·3
Tirucallone	—	—	230—231	−168·2
Lanosteryl acetate	156·5—158·8 [a]	+90·5 [a]	222—224 [b]	+54·6 [b]
Lanosterol	113—115 [a] 145 [a]	+78·3 [a]	183—184 [b]	+25·7 [b]
Lanosterone	105—107	+172·6 [a]	165—167 [b]	+121·1 [b]

[a] Ruzicka, Rey, and Muhr, *Helv. Chim. Acta*, 1944, **27**, 472. [b] Dorée, McGhie, and Kurzer, *J.*, 1948, 988. [c] McGhie, private communication.

The success attending the formation of euphatriene from euphyl toluene-*p*-sulphonate by Bennett and Warren (*loc. cit.*) was not met with on heating *tirucallyl toluene*-p-*sulphonate* which was recovered unchanged after being boiled with pyridine. The action of phosphorus oxychloride on tirucallenol gave an oily product which was hydrogenated to an oily compound, probably

tirucallene, which with chromic acid gave a yellow oil. Attempts to obtain crystalline compounds at the different stages failed. The yellow oil on catalytic hydrogenation gave colourless *dihydrotirucallane*, m. p. 139—141°, which was different from *dihydroeuphane*, m. p. 112—113°, prepared by reduction of diketoeuphene.

Experimental.

Microanalyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected.

Dihydroeuphenol.—Euphenyl acetate (15 g.) was oxidised as described previously by McDonald, Warren, and Williams (*loc. cit.*), and the diketoeuphenyl acetate crystallised from chloroform–methanol in brittle yellow needles, m. p. 106—107°, $[\alpha]_D^{20}$ +25·7° (Found : C, 76·9; H, 10·2. Calc. for $C_{32}H_{46}O_4$: C, 77·1; H, 10·1%). The light-extinction curve in hexane showed $\lambda_{max.}$ 288 mμ., log $\epsilon_{max.}$ 3·94. The acetate (1·5 g.) was boiled under reflux for 3 hours with 8% alcoholic potassium hydroxide (100 ml.). The product, crystallised several times from acetone and finally from methanol, gave *dihydroeuphenol* as yellow felted needles, m. p. 115—116°, $[\alpha]_D^{18}$ +32·1° in chloroform (*c*, 1·06) (Found : C, 78·6; H, 10·45. $C_{30}H_{44}O_3$ requires C, 78·9; H, 10·6%).

Dihydroeuphenone.—Euphenol (10 g.) in glacial acetic acid (650 ml.) was treated with chromic acid (12 g.) in 90% acetic acid (160 ml.). The solution was stirred for 6 hours at room temperature, poured into water, and extracted with ether. The ethereal solution, washed with sodium carbonate solution, gave an oil. The oil in light petroleum was filtered through activated alumina (250 g.), and the column washed with light petroleum (2·5 l.) and developed with light petroleum–benzene (8 l.). The different fractions all gave yellow oils (total weight, 6 g.) which, dissolved in acetone–methanol (1 : 1) and set aside, gave a waxy solid, which, crystallised several times from methanol at 0°, gave *dihydroeuphenone* as light yellow felted needles, m. p. 63—64°, $[\alpha]_D^{18}$ +31·1° in chloroform (*c*, 0·568) (Found : C, 79·4; H, 10·4%. $C_{30}H_{44}O_3$ requires C, 79·2; H, 10·2%).

Dihydroeuphanyl Acetate.—Diketoeuphenyl acetate (700 mg.) in glacial acetic acid (45 ml.) and platinic oxide (200 mg.) absorbed hydrogen during 30 minutes (observed, less blank : 36·9 ml. at N.T.P. Calc. for $C_{32}H_{48}O_4$: 1 mol. = 37·4 ml.). The product crystallised from chloroform–methanol to give *dihydroeuphanyl acetate* in lustrous needles, m. p. 190—191·5°, $[\alpha]_D^{20}$ −15·2° in chloroform (*c*, 1). After sublimation at 140—150° in a high vacuum, the product had m. p. 196—199° (Found : C, 76·7; H, 10·4. $C_{32}H_{48}O_4$ requires C, 76·8; H, 10·4%). It gave no colour with tetranitromethane.

Dihydroeuphanone.—(*a*) Diketoeuphanyl acetate (2·5 g.) was hydrolysed as described for diketoeuphenyl acetate. The product in benzene (75 ml.) and glacial acetic acid (15 ml.) was treated with stirring below 5° with 10% aqueous chromic acid (25 ml.) during 10 minutes, and stirring continued for 1 hour. Benzene was added to dissolve the separated tarry mass, and the solution was treated with excess of sulphur dioxide. The benzene layer, washed with aqueous sodium hydroxide and water, gave an oil which was dissolved in light petroleum and filtered through alumina (15 g.). The filtrate gave a colourless oil which, dissolved in chloroform–methanol and set aside, deposited an amorphous solid. The mother-liquors gave crystals which, crystallised 3 times from methanol, gave a small yield of *dihydroeuphanone* as colourless plates, m. p. 186—187°, $[\alpha]_D^{20}$ −144·7° in chloroform (*c*, 0·553) (Found : C, 78·8; H, 10·6. $C_{30}H_{46}O_3$ requires C, 78·95; H, 10·5%).

(*b*) Diketoeuphenone (600 mg.) in glacial acetic acid (25 ml.) was hydrogenated in the presence of Adams's catalyst (50 mg.). In 30 minutes 0·9 mol. of hydrogen had been absorbed. After 12 hours the product was crystallised from methanol to give diketoeuphanone, m. p. 185—186° undepressed when mixed with a specimen from (*a*).

Dihydroeuphane.—Euphene, obtained from euphatriene (cf. Bennett and Warren, *loc. cit.*), was oxidised to diketoeuphene as described by Roth and Jeger (*Helv. Chim. Acta*, 1949, **32**, 1625).

(*a*) Diketoeuphene (100 mg.) in glacial acetic acid (30 ml.) and zinc dust (400 mg.) were boiled for 2 hours. The ethereal extract, washed with aqueous sodium hydroxide and water, gave an oil. This oil in light petroleum was filtered through alumina (5 g.), and the colourless oil, crystallised 3 times from methanol, gave *dihydroeuphane* as colourless felted needles, m. p. 112—113° (Found : C, 81·9; H, 11·3. $C_{30}H_{52}O_3$ requires C, 81·8; H, 11·9%).

(*b*) Diketoeuphene was hydrogenated at 60 atmospheres for 6 hours in the presence of Adams's catalyst; the product, crystallised as above, gave diketoeuphane, m. p. 106—110°, undepressed when mixed with a specimen from (*a*).

Tirucallyl Toluene-p-sulphonate.—Tirucallol (1·9 g.) was treated with toluene-*p*-sulphonyl chloride (2 g.) in pyridine (10 ml.) on a water-bath. The product in dry ether was chromatographed through alumina (40 g.). Fraction (1), 50 ml., eluted a solid (0·6 g.) which crystallised from aqueous acetone to give colourless needles of *tirucallyl toluene-p-sulphonate*, m. p. 147·5—148° (Found : C, 76·4; H, 10·2; S, 5·4. $C_{37}H_{54}O_3S$ requires C, 76·5; H, 9·7; S, 5·5%). Fraction (2), 450 ml., eluted tirucallol (1·25 g.).

Tirucalladienone Oxime.—Tirucallol, treated with copper in a vacuum or with copper oxide at 300° for 10 minutes in an atmosphere of carbon dioxide, failed to give a crystalline ketone. *Tirucalladienone oxime* crystallised from methanol in large, thin laminæ, m. p. 218—220°, $[\alpha]_D^{20}$ −71·8° in chloroform (*c*, 1) (Found : C, 81·9; H, 11·3; N, 3·16. $C_{30}H_{49}ON$ requires C, 81·9; H, 11·2; N, 3·19%).

Tirucallenone. Tirucallenol (2·5 g.) was heated with copper oxide (600 mg.) at 300° for 10 minutes in an atmosphere of carbon dioxide. The reaction product in light petroleum (b. p. 50—70°; 50 ml.) was filtered through freshly activated alumina (20 g.); the material obtained from the filtrate, crystallised once from acetone and 3 times from methanol, gave *tirucallenone* as fine, colourless needles, m. p. 62—64°, $[\alpha]_D^{20}$ +40·2° in chloroform (*c*, 1·02). A depression of 15° was observed on admixture with euphenone (Found : C, 83·9; H, 11·6. $C_{30}H_{48}O$ requires C, 84·45; H, 11·8%). *Tirucallenone oxime* crystallised from ethanol in pearly plates, m. p. 236·5—237·5°, $[\alpha]_D^{20}$ −66° in chloroform (*c*, 1) (Found : C, 81·2; H, 11·5; N, 2·66. $C_{30}H_{51}ON$ requires C, 81·6; H, 11·6; N, 3·16%). *Tirucallenone semicarbazone* crystallised once from ethanol and 3 times from acetone–methanol as pearly plates, m. p. 214—215°

$[\alpha]_D^{20}$ −10·5° in chloroform (*c*, 1·05) (Found: C, 76·9; H, 10·9; N, 9·2. $C_{31}H_{53}ON$, requires C, 77·6; H, 11·05; N, 8·7%).

Diketotirucallenol.—Tirucallenyl acetate (4·5 g.) was oxidised with chromic acid (4·5 g.) as above. The product in light petroleum (b. p. 50—70°) was filtered through alumina (150 g.) and developed successively with the same solvent (5 l.), light petroleum–benzene (5 : 1; 3 l.) and finally light petroleum–benzene (1 : 1; 2 l.) to give yellow crystals (2·6 g.) with m. p. varying between 126° and 132°. Crystallisation from chloroform–methanol and finally from methanol gave *diketotirucallenyl acetate* as yellow brittle needles, m. p. 135—136°, $[\alpha]_D^{20}$ −17·1° in chloroform (*c*, 1·17) (Found: C, 77·2; H, 10·1. $C_{32}H_{50}O_4$ requires C, 77·05; H, 10·1%). Light-extinction curve in hexane showed $\lambda_{max.}$ 267 mμ, log $\epsilon_{max.}$ 3·98. The acetate (1 g.) was refluxed with 8% alcoholic potassium hydroxide (150 ml.) for 3 hours and gave, on crystallisation from methanol, *diketotirucallenol* as yellow felted needles, m. p. 136—137°, $[\alpha]_D^{20}$ −24·5° in chloroform (*c*, 1) (Found: C, 78·9; H, 10·6. $C_{30}H_{44}O_3$ requires C, 78·9; H, 10·6%). Reacetylation with pyridine and acetic anhydride gave diketotirucallenyl acetate, m. p. 135—136°, undepressed on admixture with original specimen.

Diketotirucallanol.—Diketotirucallenyl acetate (600 mg.) was hydrogenated as above (observed: 25 ml. at N.T.P. Calc. for $C_{32}H_{50}O_4$: 1 mol. = 26·9 ml.). The product crystallised from chloroform–methanol to give *diketotirucallenyl acetate* in brittle laminæ, m. p. 222—224°, $[\alpha]_D^{20}$ −131° in chloroform (*c*, 0·63) (Found: C, 77·1; H, 10·6. $C_{32}H_{52}O_4$ requires C, 76·8; H, 10·4%). It gave no colour with tetranitromethane. The acetate (200 mg.) was refluxed for 3 hours with 8% alcoholic potassium hydroxide (50 ml.). The product was crystallised 6 times from methanol to give *diketotirucallanol* as white felted needles, m. p. 199—200°, $[\alpha]_D^{20}$ −144·3° in chloroform (*c*, 0·82) (Found: C, 78·6; H, 10·4. $C_{30}H_{48}O_3$ requires C, 78·9; H, 11·0%).

Diketotirucallanone.—Diketotirucallanol (400 mg.) in benzene (15 ml.) and glacial acetic acid (2·5 ml.) was treated with 10% aqueous chromic acid (2·5 ml.) at a temperature below 5° and stirred for 1 hour. The same procedure in working up the product was adopted as that described for diketoeuphanone above. The reaction product was taken up in methanol and acetone, and crystallised 4 times from acetone, to give *diketotirucallanone* as colourless needles, m. p. 230—231°, $[\alpha]_D^{20}$ −168·2° in chloroform (*c*, 0·56) (Found: C, 77·7; H, 10·5%). After sublimation at 160° in high vacuum, the ketone had m. p. 220—224° (Found: C, 78·7; H, 10·5. $C_{30}H_{46}O_3$ requires C, 78·95; H, 10·5%).

Diketotirucallane.—Phosphorus oxychloride (5 ml.) was added slowly with shaking to a solution of tirucallenol (3·0 g.) in pyridine (30 ml.), then heated on a water-bath for 1½ hours, and boiled for 5 minutes. The cold solution was poured slowly on crushed ice and extracted with ether. The ethereal solution, washed with concentrated hydrochloric acid and then with water until neutral, gave a yellow oil which was run in light petroleum through a column of alumina (30 g.). A colourless oil resulted, which could not be crystallised. This oil (1·5 g.), in a mixture of glacial acetic acid and ethyl acetate (100 ml.), was shaken for 12 hours with Adams's catalyst (50 mg.) and hydrogen at 120°/50 atmospheres. The product was again a yellow oil which, dissolved in light petroleum (250 ml.) and chromatographed through alumina (100 g.), gave only colourless glassy oils which could not be crystallised. The hydrogenated oil (1·3 g., 1 mol.) in acetic acid (30 ml.) was treated with chromic acid (1·3 g., 4 mols.) in 90% acetic acid at 90° for 4 hours. The neutral product in light petroleum run through alumina gave a few yellow crystals, m. p. 114—116°, but the main eluate was obtained as a yellow oil. This (200 mg.) was reduced by amalgamated zinc in boiling acetic acid, the product in light petroleum filtered through alumina (5 g.) and crystallised 6 times from methanol, to give *diketotirucallane* as colourless felted needles, m. p. 139—141° (Found: C, 81·8; H, 10·8. $C_{30}H_{48}O_2$ requires C, 81·8; H, 10·9%).

Tirucallyl Acetate Dibromide.—Tirucallyl acetate (1·6 g.) in carbon tetrachloride (15 ml.) was treated with a 3% solution (20 ml.) of bromine in the same solvent; the bromine was smoothly absorbed. The solvent was removed under reduced pressure and the product crystallised 3 times from acetone, to give *tirucallyl acetate dibromide* as colourless plates, m. p. 150—160° (Found: C, 61·5; H, 8·4; Br, 25·2. $C_{32}H_{52}O_2Br_2$ requires C, 61·2; H, 8·3; Br, 25·4%).

Monobromotirucallol.—The above dibromide (1·5 g.) was refluxed with 3% alcoholic potassium hydroxide (100 ml.) for 4 hours and then poured into water. The insoluble product was crystallised from acetone–methanol (1 : 1) to give *monobromotirucallol* as colourless plates, m. p. 179—180° (Found: C, 71·1; H, 9·9; Br, 15·1. $C_{30}H_{49}OBr$ requires C, 71·3; H, 9·7; Br, 15·8%). *Monobromotirucallyl acetate*, obtained from the alcohol (400 mg.) by boiling it with acetic anhydride and pyridine, crystallised from acetone–methanol as colourless needles, m. p. 173—174° (Found: C, 70·5; H, 9·2; Br, 15·2. $C_{32}H_{51}O_2Br$ requires C, 70·2; H, 9·4; Br, 14·6%).

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324. *Anhydrides of Polyhydric Alcohols. Part XIV. Observations on the Ring Scission of* 1 : 2-5 : 6-*Diepoxyhexane and* 3 : 4-iso*Propylidene* 1 : 2-5 : 6-*Dianhydromannitol.*

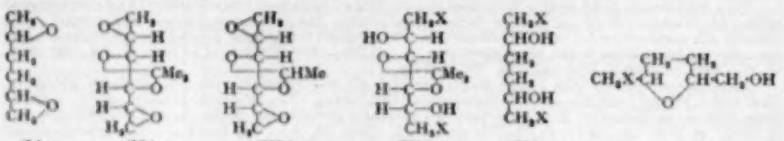
By L. F. Wiggins and D. J. C. Wood.

1 : 2-5 : 6-Diepoxyhexane (I) has been prepared in good yield by treatment of hexa-1 : 5-diene with perbenzoic acid. This reactive diepoxy-compound undergoes ring scission through the action of various reagents with the formation of either cyclic or straight-chain products. Water causes ring scission of (I) and gives rise to 2 : 5-bishydroxymethyltetrahydrofuran. Hydrochloric acid and (I) furnish 2-chloromethyl-5-hydroxymethyltetrahydrofuran; ammonia and (I) give what is believed to be 5-hydroxy-2-hydroxymethylpiperidine. When treated with methylmagnesium iodide (I) gives 1 : 6-di-iodo-2 : 5-dihydroxyhexane. The analogous diepoxide, 3 : 4-*iso*propylidene 1 : 2-5 : 6-dianhydromannitol (II) behaves similarly with the Grignard reagent and also suffers ring scission with reagents such as water, sodium methoxide, hydrochloric acid, and ammonia (see also Wiggins, *J.*, 1946, 384). The reactions of both of the above diepoxides with lithium aluminium hydride are also described.

In view of the interest currently being shown in diepoxy-compounds it seems opportune to describe the results of our work on the chemical properties of two such compounds, 1 : 2-5 : 6-diepoxyhexane (I) and 3 : 4-*iso*propylidene 1 : 2-5 : 6-dianhydromannitol (II). Wiggins (*loc. cit.*) has demonstrated the extreme lability of the epoxide rings of (II) towards both acidic and alkaline reagents. 3 : 4-Ethylidene 1 : 2-5 : 6-dianhydromannitol (III) was studied and in this also the epoxide rings were shown to be very readily attacked by hydrolytic agents. Because of the interesting properties of (II) and (III) the simpler analogue, 1 : 2-5 : 6-diepoxyhexane (I), was prepared, its reactions towards various reagents examined, and its behaviour compared with that of the mannitol derivatives, (II) and (III).

Bigot (*Ann. Chim.*, 1891, **22**, 441, 447) treated epichlorohydrin with sodium and obtained a liquid of formula $C_6H_{10}O_2$ which he believed to be "diallyl dioxide." Przybytek (*Ber.*, 1885, **18**, 1352) treated hexa-1 : 5-diene with hypochlorous acid and obtained "dichlorohexyleneglycol" from which, on treatment with potassium hydroxide, was produced a liquid of the same composition. The reported properties and reactions of these two products suggested that they may have been essentially (I) but no evidence was advanced by either of these workers, nor has any been reported since, which proved the structure of their products.

1 : 2-5 : 6-Diepoxyhexane (I) has now been prepared by the smooth oxidation of hexa-1 : 5-diene with perbenzoic acid. The diepoxide is readily isolated and purified and may be obtained in about 70% yield.



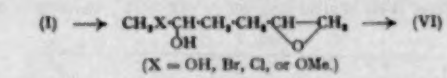
(I) (II.) (III.) (IV.) (V.) (VI.)

(X = OH, Cl, OMe, etc.)

It is clear that three isomeric forms of (I) are theoretically possible and that this preparation should give a mixture of a *meso*- or *cis*-form and a *racemic* or *trans*-form composed of two enantiomorphs. That such a mixture is actually formed when hexa-1 : 5-diene is oxidised with perbenzoic acid is demonstrated by the fact that whenever crystalline materials are isolated from a reaction carried out on the product, they are invariably found to be mixtures of isomers. It has not been possible to show, when liquid reaction products are obtained, that these are also mixtures of isomers, but it is likely that the individual constituents would have closely similar boiling points and indeed be extremely difficult to separate.

It has been found (Wiggins, *loc. cit.*) that each ethylene oxide ring in the 1 : 2-5 : 6-dianhydro-derivatives, (II) and (III), of mannitol reacted quite independently of the other, ring scission leading to the addition of the anionic part of the hydrolytic agent to the mannitol molecule at C_1 and C_6, giving rise to compounds of type (IV). It has been found, however, that 1 : 2-5 : 6-diepoxyhexane (I) behaves differently inasmuch as it gives rise to two distinct types of reaction product, depending on the nature of the reagent used; namely, (*a*) derivatives of hexane-2 : 5-diol (V), and (*b*) 2 : 5-disubstituted derivatives of tetrahydrofuran (VI). Type (*a*) must arise in

a similar way to the ring scission products of 1 : 2-5 : 6-dianhydromannitol derivatives; type (*b*) are all such that one of the substituents at C_3 or C_4 of the tetrahydrofuran ring is a hydroxymethyl group whilst the other is a methyl group substituted by the anionic part of the reagent used. The occurrence of type (*b*) products may be explained on the assumption, supported by statistical considerations, that the reagent attacks one oxide ring first, producing a monoepoxy-derivative; the hydroxyl group liberated at one end of the molecule then immediately effects cleavage of the residual ethylene oxide ring, thereby forming the tetrahydrofuran nucleus:



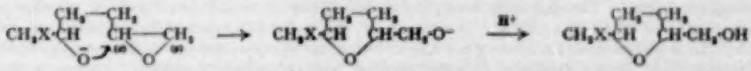
(X = OH, Br, Cl, or OMe.)

A third type of product, a piperidine derivative, has been obtained in one instance (the reaction of diepoxyhexane with ammonia), but its formation is explicable by a modification of the foregoing remarks.

The reasons why type (*b*) reaction does not always occur is not clear, but certain explanations suggest themselves. There is undoubtedly a tendency for any suitable 2 : 5-disubstituted hexane to undergo ring closure to form a tetrahydrofuran derivative, as is shown by the ease with which hexane-2 : 5-diol itself is converted into 2 : 5-dimethyltetrahydrofuran. The suppression of this tendency may be due to one of the following causes: (i) the addition of the group X at C_3 and C_4 instead of at C_1 and C_2. (ii) the inability of the hydroxyl group formed on scission of the first ring to attack the second ring, the latter subsequently being opened by another molecule of reagent.

With regard to (i), most published work relating to scission of oxide rings located at the end of a carbon chain has shown that the anionic part of the attacking reagent combines with the terminal carbon atom. Some evidence has, however, been given supporting the alternative effect; for example, Swern, Billen, and Knight (*J. Amer. Chem. Soc.*, 1949, **71**, 1152) have shown that the acid-catalysed reaction of propylene oxide with allyl alcohol can give rise to 2-allyloxypropan-1-ol in addition to the normal product of the alkali-catalysed reaction, 1-allyloxypropan-2-ol, and that 3 : 4-epoxybut-1-ene gives chiefly the primary alcohol when treated with allyl alcohol under alkaline or acid conditions. Nevertheless, in the work now described no experimental evidence has been forthcoming to support the theory of secondary carbon-atom addition during the ring scission of diepoxyhexane; in fact considerable evidence to the contrary has been obtained.

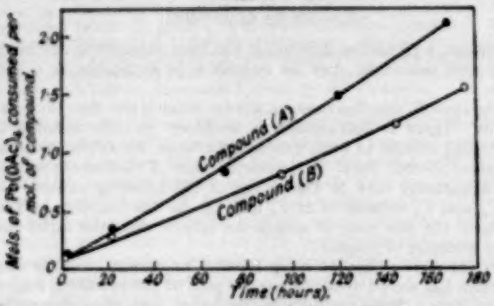
The effect outlined in (ii) above might be due to some influence exerted by the group X attached to the terminal carbon atom, but a more probable explanation arises from the observation that tetrahydrofuran derivatives result only when reactions with the diepoxide (I) are carried out in polar solvents, *e.g.*, water and methanol, whilst open-chain compounds are invariably formed from reactions in non-polar media, such as benzene or ether. This suggests that intramolecular scission of the second oxide ring will follow scission of the first ring only when the hydroxyl group formed during this initial stage is able to ionise to some extent; if this were the case then a difference between the courses of reactions in polar and in non-polar solvents would be expected. It is of significance that whilst diepoxyhexane readily undergoes ring scission with ammonia in methyl alcohol, it is quite unaffected by ammonia in ethereal solution. The real course of reaction (*b*) may be:



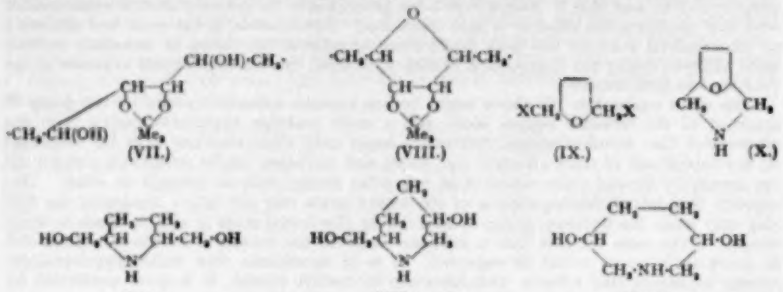
The scission of the second epoxide ring by the oxide anion may have operated either at (*α*) or at (*γ*). Previous experience in the sugar series has shown that (*γ*) should have been the main point of attack; it can only be surmised that the possibility of formation of a five-membered ring outweighed this tendency. The formation of tetrahydrofuran derivatives from 3 : 4-*iso*propylidene 1 : 2-5 : 6-dianhydromannitol is, of course, precluded by the presence of the *iso*propylidene group itself; this orientates the addenda of the dioxa*cyclo*pentane ring formed by this residue at C_3 and C_4 of the mannitol molecule in such a way [see (VII)] as to make ring closure impossible. From scale-model studies it would appear, however, that ring closure between C_3 and C_5 could occur in, for example, 3 : 4-*iso*propylidene talitol to give (VIII), though such a compound is as yet unknown.

When (I) was treated with boiling water a liquid (*A*) resulted. It might be expected that when hydrolysis of the oxide rings occurred it would lead to the formation of 1 : 2 : 5 : 6-tetrahydroxyhexane but the product actually obtained showed properties which did not agree with this contention. When treated with lead tetra-acetate (according to Hockett and McClenahan's procedure, *J. Amer. Chem. Soc.*, **1939, 61**, 1667) the liquid (*A*) showed a slow consumption of reagent, a behaviour not at all indicative of the presence of two glycol groups (see Fig. 1). Treatment of (*A*) with toluene-*p*-sulphonyl chloride in pyridine solution furnished a crystalline ditoluene-*p*-sulphonyl derivative of bishydroxymethyltetrahydrofuran, which after three recrystallisations from alcohol had m. p. 113—118°, showing it to be a mixture.

FIG. 1.



2 : 5-Di(toluene-*p*-sulphonyloxymethyl)tetrahydrofuran (IX; X = TsO) (Newth and Wiggins, *J.*, **1948**, 155) has m. p. 128°, and the m. p. of a mixture of the two derivatives was found to lie between the two individual values. The *X*-ray powder photographs of the two substances were



indistinguishable. The ditoluene-*p*-sulphonyl derivative of liquid (*A*) therefore consists at least partly of (IX; R = TsO). Treatment of the toluene-*p*-sulphonyl derivative of (*A*) with sodium iodide in dry acetone gave rise to two equivalents of sodium toluene-*p*-sulphonate indicating that both toluene-*p*-sulphonyl residues were attached to primary carbon atoms. Final proof that the toluene-*p*-sulphonyl derivative of (*A*) contained (IX; X = TsO) was given by its reaction with methyl-alcoholic ammonia, which afforded 8-oxa-3-aza*bicyclo*[3 : 2 : 1]-octane (X) (Newth and Wiggins, *loc. cit.*). This was confirmed by the preparation of the toluene-*p*-sulphonate, picrate, and oxalate, all of which had properties in agreement with those recorded by Newth and Wiggins.

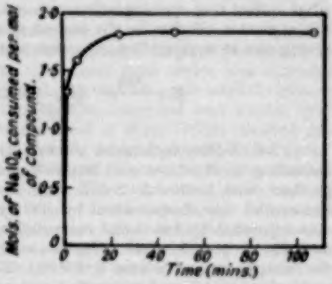
The toluene-*p*-sulphonyl derivative of (*A*) was separated by fractional crystallisation, with some difficulty, into two constituents, one having m. p. 118—122°, undepressed on admixture with (IX; X = TsO), and the other having m. p. 96—99° and the same composition, $C_{26}H_{28}O_7S_2$. Efforts further to separate these into products of sharper melting point were unsuccessful.

The fact that the toluene-*p*-sulphonyl derivative of (*A*) proved to be a mixture provides support for the postulated existence of 1 : 2-5 : 6-diepoxyhexane (I) as a mixture of isomers. The derivative (IX; X = TsO) can theoretically exist in *cis*- and *trans*-forms, and these are doubtless represented by the two products, m. p. 96—99° and m. p. 116—122°; from this it can be inferred that the liquid (*A*) consists of the *cis*- and the *trans*-form of 2 : 5-bishydroxymethyltetrahydrofuran. The 2 : 5-bishydroxymethyltetrahydrofuran obtained by Newth and Wiggins (*loc. cit.*) by the hydrogenation of 5-hydroxymethylfurfuraldehyde would appear, on the other hand, to be one distinct isomer (although it is not yet possible to state which) because its toluene-*p*-sulphonyl derivative, obtained in good yield, possessed a sharp melting point. This is difficult to explain because it would be expected that addition of hydrogen to the planar furan ring would lead to the production of a mixture of approximately equal amounts of the *cis*- and the *trans*-2 : 5-disubstituted tetrahydrofuran.

Since the liquid (*A*) has now been shown to be 2 : 5-bishydroxymethyltetrahydrofuran the structure of the diepoxyhexane from which it was obtained must follow as (I). The other possible structures for the diepoxide, namely 1 : 6-2 : 5 or 1 : 5-2 : 6, cannot be correct because five-, six-, or seven-membered oxide rings could not undergo ring scission under such mild conditions as obtain here.

The action of water on 3 : 4-*iso*propylidene 1 : 2-5 : 6-dianhydromannitol (II) has now also been studied. Wiggins (*loc. cit.*) showed that the oxide rings in this compound were very labile to both acid and alkaline reagents, but did not investigate the action of boiling water alone. This reaction has now been found to yield 3 : 4-*iso*propylidene mannitol. Cyclisation to a tetrahydrofuran derivative is not possible for reasons already given.

FIG. 2.



When (I) was treated with fuming hydrochloric acid a violent reaction occurred and only tarry matter was obtained. The diepoxide reacted vigorously with concentrated hydrochloric acid, but a smooth reaction occurred with dilute acid although some heat was generated. The product (*B*) isolated has been shown to be 2-chloromethyl-5-hydroxymethyltetrahydrofuran (VI; X = Cl). When treated with lead tetra-acetate this compound exhibited closely similar behaviour to the bishydroxymethyltetrahydrofuran (*A*) (see Fig. 1), indicating the absence of vicinal hydroxy-groups and suggesting the presence of the tetrahydrofuran nucleus. Proof of this structure was afforded by the fact that treatment with thionyl chloride in pyridine gave 2 : 5-bischloromethyltetrahydrofuran (IX; X = Cl) having constants in agreement with those recorded by Newth and Wiggins (*loc. cit.*) for the product of the direct chlorination of 2 : 5-bishydroxymethyltetrahydrofuran.

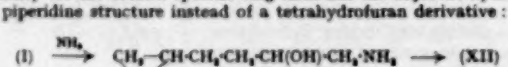
With methyl alcoholic sodium methoxide, (I) gave a compound shown to be 5-hydroxymethyl-2-methoxymethyltetrahydrofuran (VI; X = OMe) by its conversion into 2 : 5-bismethoxymethyltetrahydrofuran (IX; X = OMe), which was synthesised for comparison by the direct methylation of 2 : 5-bishydroxymethyltetrahydrofuran.

When (I) was treated with methyl alcoholic ammonia a basic liquid (*C*) was obtained; this was shown to have the formula $C_6H_{13}O_3N$, and the structure, 5-hydroxy-2-hydroxymethylpiperidine (XII), has tentatively been assigned. This formed a liquid triacetyl derivative containing two acetyl groups hydrolysable with alkali; thus the derivative contained two *O*-acetyl groups and one *N*-acetyl group. Evidence for the inclusion of the nitrogen atom in the heterocyclic ring and the rejection of a tetrahydrofuran-type structure arises from the fact that oxidation of the base (*C*) with sodium periodate proceeds rapidly with the consumption of two equivalents of oxygen (see Fig. 2). If the hetero-atom in the ring system were oxygen, no such oxidation would take place because it has been shown that the grouping $HO\cdot CH_2\cdot \overset{|}{C}H\cdot O\cdot \overset{|}{C}H\cdot$ does not react with periodate under the conditions employed (see Jackson, "Organic Reactions," Vol. II, page 341; John Wiley, 1947). Conclusive evidence that the nitrogen atom was heterocyclic was provided by the fact that no nitrogen was evolved on treatment of (*C*) with nitrous acid; indeed a *N*-nitroso-derivative responding to the Liebermann test was obtained. Thus, on the basis of the above facts, three structures only, (XI), (XII), and (XIII), are possible for the base (*C*).

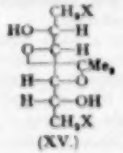
Treatment of the base (*C*) with toluene-*p*-sulphonyl chloride gave a hard glass which was probably a tritoluene-*p*-sulphonyl derivative; the fact that this product showed a neutral reaction in aqueous alcoholic solution indicated that the heterocyclic imino-group had undergone toluene-*p*-sulphonation in addition to the hydroxyl groups. On being treated with sodium iodide in acetone solution this compound yielded 1·2 moles of sodium toluene-*p*-sulphonate, and a product containing nitrogen, sulphur, and iodine. This indicated that only one toluene-*p*-sulphonyloxy-group was attached to a primary carbon atom. From theoretical considerations it appears impossible that the *N*-toluene-*p*-sulphonyl group could react with sodium iodide, but, in order to confirm this, *N*-toluene-*p*-sulphonylpiperidine was treated with sodium iodide under the usual conditions; no sodium toluene-*p*-sulphonate was obtained. Of the three possible structures postulated above (XI) would give a toluene-*p*-sulphonyl derivative in which two sulphonyloxy-residues could be replaced by sodium iodide whilst (XIII) would give a derivative containing no replaceable sulphonyloxy-residues. Only (XII) would yield a derivative which contained a single primary toluene-*p*-sulphonyl group.

The action of acetic anhydride in methyl alcohol on (*C*) gave a liquid *N*-acetyl derivative, which on treatment with toluene-*p*-sulphonyl chloride yielded a partly crystalline ditoluene-*p*-sulphonyl compound. This, with sodium iodide in acetone solution, gave rise to one equivalent of sodium toluene-*p*-sulphonate. This is in agreement with the preceding evidence, and in view of these facts we tentatively ascribe to the base (*C*) the structure (XII). Further work designed to prove this structure conclusively is being carried out.

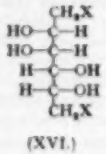
The formation of (XII) from (I) can be explained if it is assumed that one of the epoxide rings suffers ring opening with ammonia giving a monoamine (XIV), the amino-group of which has a greater affinity for the second epoxide ring than has the adjacent hydroxyl group, thus giving rise to a piperidine structure instead of a tetrahydrofuran derivative:



1 : 2-5 : 6-Diepoxyhexane reacted smoothly with lithium aluminium hydride employed according to Nystrom and Brown's procedure (*J. Amer. Chem. Soc.*, 1947, **69**, 1197). The product was hexane-2 : 5-diol, and no tetrahydrofuran derivative was encountered. The hexanediol was characterised by the formation of a crystalline ditoluene-*p*-sulphonate, which was separated by fractional recrystallisation into two isomeric compounds, (i) m. p. 71—74°, and (ii), m. p. 113—114°. These are doubtless the ditoluene-*p*-sulphonates of the *meso*- and the racemic form of hexane-2 : 5-diol. The same two crystalline toluene-*p*-sulphonyl derivatives were obtained from hexane-2 : 5-diol prepared by hydrogenation of acetonylacetone in the presence of copper chromite (Hill and Adkins, *J. Amer. Chem. Soc.*, 1938, **60**, 1033). In addition, the lower-melting isomeride was found to be identical with a toluene-*p*-sulphonyl derivative obtained by Newth and Wiggins (unpublished) from the acetolysis product of 2 : 5-dimethyltetrahydrofuran. Here again it is interesting to note the isolation of two isomerides from the reaction with diepoxyhexane whilst the production of the same compound from a furan derivative yields only one of them.



(XV.)



(XVI.)

3 : 4-*iso*Propylidene 1 : 2-5 : 6-dianhydromannitol reacted similarly with lithium aluminium hydride giving 3 : 4-*iso*propylidene 1 : 6-dideoxymannitol (XV; X = H). The structure of this product followed from the fact that acid hydrolysis furnished 1 : 6-dideoxymannitol (XVI; X = H), identical with that obtained by Wiggins (*Nature*, 1949, **164**, 672) by the sodium-amalgam reduction of 1 : 6-dichloro 1 : 6-dideoxymannitol, and by Micheel (*Annalen*, 1932, **496**, 96) by the action of molecular silver on 1 : 6-dichloro 2 : 4-3 : 5-dimethylene 1 : 6-dideoxymannitol and subsequent hydrolysis.

The action of Grignard reagents on oxide-ring compounds has been investigated by several authors, notably by Blaise (*Compt. rend.*, 1902, **134**, 557) and by Grignard himself (*ibid.*, 1903,

136, 1260); ethylene oxide, for example, was found to react with ethylmagnesium bromide to give chiefly ethylene bromohydrin. When 1 : 2-5 : 6-diepoxyhexane was treated with methylmagnesium iodide in ether a mixture of two isomeric crystalline di-iododihydroxyhexanes was formed. This was easily separated, by virtue of the different solubilities of the constituents in ether, into an isomer of m. p. 94—95° and one of m. p. 116—117°. These are assumed to be the *meso*- and the racemic form of 1 : 6-di-iodo-2 : 5-dihydroxyhexane (V; X = I). It was hoped that confirmation of this could be accomplished by the preparation of a ditoluene-*p*-sulphonyl derivative and its subsequent treatment with sodium iodide, but an attempt to prepare such a derivative in pyridine solution led only to the formation of a liquid product which contained free iodine. The same result followed attempts to acetylate and benzoylate the iodo-compound. Evidence providing considerable support for the structure was, however, obtained from the reaction of 3 : 4-*iso*propylidene 1 : 2-5 : 6-dianhydromannitol with methylmagnesium iodide. This led to the formation of 1 : 6-di-iodo 3 : 4-*iso*propylidene 1 : 6-dideoxymannitol (XV; X = I), the structure of which was proved by hydrolysis with acid to give 1 : 6-di-iodo 1 : 6-dideoxymannitol (XVI; X = I) (identical with that obtained by Wiggins *J.*, 1946, 384), and subsequent conversion of this into 1 : 6-di-iodo 2 : 4-3 : 5-dimethylene 1 : 6-dideoxymannitol (Micheel, *loc. cit.*). Since 1 : 2-5 : 6-diepoxyhexane has been shown to behave in an exactly analogous manner to 3 : 4-*iso*propylidene 1 : 2-5 : 6-dianhydromannitol towards lithium aluminium hydride, it appears legitimate to extend the analogy to the reactions with methylmagnesium iodide (which itself resembles the hydride in many respects); hence it may be inferred that in the latter case scission of the oxide rings in diepoxyhexane occurs in the normal way giving 1 : 6-di-iodo-2 : 5-dihydroxyhexane.

The iodine atoms in 1 : 6-di-iodo-2 : 5-dihydroxyhexane were quite labile and were hydrolysed by being heated with water, addition of silver nitrate giving a copious precipitate of silver iodide. For this reason recrystallisation of the compound from water was attended by considerable losses, but no suitable alternative was found, the usual organic solvents causing separation of free iodine on being heated. When the di-iodo-compound was heated with silver acetate in aqueous alcoholic solution a quantitative yield of silver iodide resulted and a liquid product was obtained. This was found to be 2 : 5-bishydroxymethyltetrahydrofuran; the course of this reaction was doubtless through 1 : 2-5 : 6-diepoxyhexane, formed by removal of the elements of hydrogen iodide from the di-iodo-compound, which subsequently reacted with water in the manner already established. Repetition of the experiment in absolute alcoholic solution furnished isolable 1 : 2-5 : 6-diepoxyhexane (I). 1 : 6-Di-iodo 3 : 4-*iso*propylidene 1 : 6-dideoxymannitol was found to behave in quite an analogous manner to 1 : 6-di-iodo-2 : 5-dihydroxyhexane. When it was heated with silver acetate in absolute alcoholic solution, a liquid product was formed which was identified as 3 : 4-*iso*propylidene 1 : 2-5 : 6-dianhydromannitol.

Experimental.

Treatment of Hexa-1 : 5-diene with Perbenzoic Acid.—To a solution of perbenzoic acid (25·7 g., 2·3 mols.) (Braun, *Org. Synth.*, Coll. Vol. I, 431) in chloroform (430 c.c.) at 0° hexa-1 : 5-diene (9·5 c.c., 1 mol.) (Cortese, *J. Amer. Chem. Soc.*, 1929, **51**, 2266) was added; the solution was kept at 0° with occasional shaking during the first hour. Portions (2 c.c.) of the solution were withdrawn at intervals; each was added to potassium iodide (about 0·5 g.) dissolved in water (10 c.c.) acidified with acetic acid, and the liberated iodine titrated with 0·0197*N*-sodium thiosulphate solution. The consumption of perbenzoic acid (mols. per mol. of hexadiene) was as follows:

Time, hrs.	0·25	1·25	2·75	7·0	22·5	51	119	191
Consumption	0·30	0·85	1·07	1·39	1·70	1·76	1·79	1·82

When the reaction was complete, the chloroform solution was washed three times with 10% sodium hydroxide solution (100 c.c. portions) and water, and dried ($MgSO_4$). Evaporation gave a residue (9·1 g.) which, distilled under reduced pressure, afforded 1 : 2-5 : 6-*diepoxyhexane* as a colourless oil (6·0 g., 66%) with a faint, pleasant odour; b. p. 86—88°/15 mm., n_D^{25} 1·4445 (Found: C, 63·0; H, 8·6. $C_6H_{10}O_2$ requires C, 63·1; H, 8·8%).

Action of Water on 1 : 2-5 : 6-*Diepoxyhexane.*—Diepoxyhexane (2·6 g.) was heated under reflux with water (100 c.c.) for 18 hours and the solution was then concentrated under reduced pressure to a viscous syrup (2·9 g.) from which the last traces of water were removed by azeotropic distillation with benzene. Distillation of the product under reduced pressure gave a colourless viscous syrup (*A*) (1·9 g., 64%), b. p. (bath temp.) 145—149°/0·05 mm., n_D^{24} 1·4810 (Found: C, 54·2; H, 9·6. $C_6H_{14}O_4$ requires C, 54·6; H, 9·1%).

Oxidation of Syrup (A) *by Lead Tetra-acetate.*—The syrup (*A*) (0·0307 g.) was treated with an excess (50 c.c.) of a solution of lead tetra-acetate in glacial acetic acid; the consumption (Fig. 1) of oxidising agent was measured by titration of aliquot portions with sodium thiosulphate solution according to Hockett and McClenahan's general procedure (*loc. cit.*).

Treatment of Syrup (A) *with Toluene-p-sulphonyl Chloride.*—The syrup (*A*) (0·45 g.) was dissolved

in dry pyridine (10 c.c.) and toluene-*p*-sulphonyl chloride (2·0 g.) was added at 0°. After being kept overnight at 30° the solution was poured into water; the solid product (1·5 g.) was collected, washed with water, and recrystallised from alcohol, from which it separated in fine needles (0·63 g.), m. p. 98—110° (Found: C, 54·6; H, 5·5; S, 13·6. $C_{26}H_{34}O_7S_3$ requires C, 54·6; H, 5·5; S, 14·6%). Further recrystallisations from the same solvent gave a product, m. p. 113—118°. An admixture of this with 2 : 5-bishydroxymethyltetrahydrofuran ditoluene-*p*-sulphonate, m. p. 128°, prepared by Newth and Wiggins's method (*loc. cit.*) had m. p. 118—124° with shrinkage at 108—118°.

By fractional recrystallisation from a large volume of alcohol, the toluene-*p*-sulphonyl derivative was with difficulty separated into two fractions: (i) m. p. 116—122° unchanged after further recrystallisation and undepressed on admixture with Newth and Wiggins's compound (*loc. cit.*); (ii) m. p. 96—99° also unchanged by further recrystallisation (Found: C, 54·3; H, 5·2. $C_{26}H_{34}O_7S_3$ requires C, 54·6; H, 5·5%).

Action of Sodium Iodide on the Toluene-p-sulphonyl Derivative of (A).—The toluene-*p*-sulphonyl derivative (0·264 g.), m. p. 98—110°, was heated with anhydrous sodium iodide (0·75 g.) and dry acetone (10 c.c.) in a sealed tube at 105—110° for 5 hours. The precipitated sodium toluene-*p*-sulphonate was collected, washed with a little dry acetone, and dried at 110°. Yield, 0·234 g., 2·01 equivs.

Treatment of the Toluene-p-sulphonyl Derivative of (A) *with Methyl Alcoholic Ammonia.*—The toluene-*p*-sulphonyl derivative (5·0 g.), m. p. 98—110°, was heated with dry methyl alcoholic ammonia (600 c.c.; saturated at 0°) in an autoclave at 160—170° for 24 hours. The methyl alcohol was evaporated in an atmosphere of nitrogen, and the residue was heated with a solution of barium hydroxide (5·4 g.) in water (70 c.c.) on the water-bath at 80—90° for 1 hour; the water was then removed under reduced pressure and the residue dried by evaporation with benzene. The solid was extracted under reflux four times with chloroform; the extract was dried ($MgSO_4$) and evaporated to a brown syrup (1·2 g.). Distillation of this material at atmospheric pressure yielded 8-oxa-3-aza*bicyclo*[3 : 2 : 1]octane (0·32 g.), b. p. (bath temp.) 195—200°, n_D^{25} 1·4865 (Newth and Wiggins, *loc. cit.*, record b. p. 176—178°, n_D^{15} 1·4883). The toluene-*p*-sulphonate crystallised from alcohol–ether in needles, m. p. 200—202°, undepressed on admixture with an authentic specimen; the picrate gave yellow plates, m. p. 188—190°, from alcohol (the original authors record m. p. 188—189°); and the oxalate formed prisms (from alcohol), m. p. 261—262° alone or in admixture with an authentic specimen.

Action of Water on 3 : 4-iso*Propylidene* 1 : 2-5 : 6-*Dianhydromannitol.*—*iso*Propylidene dianhydromannitol (0·5 g.) (Wiggins, *J.*, 1946, 384) was heated under gentle reflux with water (30 c.c.) for 7 hours; the solution was then evaporated under reduced pressure to a syrup (0·7 g.) which, after being dried by evaporation with benzene, crystallised completely. Recrystallisation from acetone–benzene gave 3 : 4-*iso*propylidene mannitol (0·41 g., 67%) in colourless needles, m. p. 80—81° alone or in admixture with an authentic specimen.

Action of Hydrochloric Acid on 1 : 2-5 : 6-*Diepoxyhexane.*—Diepoxyhexane (1·5 g.) was diluted with water (15 c.c.) and added to concentrated hydrochloric acid (15 c.c.). The solution was heated on the water-bath for 4 hours, then neutralised with sodium hydrogen carbonate and extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated to an oil (1·6 g.) which was distilled under reduced pressure, giving 2-*chloromethyl-5-hydroxymethyltetrahydrofuran* (B) as a colourless oil (0·9 g., 46%), b. p. (bath temp.) 152—158°/15 mm., n_D^{25} 1·4540 (Found: C, 47·3; H, 7·7; Cl, 25·1; OH, 11·6. $C_5H_{11}O_3Cl$ requires C, 47·8; H, 7·3; Cl, 23·6; OH, 11·3%).

Action of Lead Tetra-acetate on 2-*Chloromethyl-5-hydroxymethyltetrahydrofuran.*—The chloro-compound (0·0304 g.) was treated with lead tetra-acetate in glacial acetic acid. The uptake of the reagent is recorded in Fig. 1.

Treatment of 2-*Chloromethyl-5-hydroxymethyltetrahydrofuran with Thionyl Chloride.*—The chloro-compound (1·3 g.) was dissolved in dry pyridine (4 c.c.) and thionyl chloride (1·5 c.c.) added dropwise with shaking and cooling in an ice-bath. A few grains of anhydrous magnesium sulphate were added and the mixture was heated on an oil-bath at 100° for 2½ hours. The product was poured into ice-water and extracted with ether; the extract was washed with dilute sodium hydrogen carbonate solution and with water, dried ($MgSO_4$), and evaporated to an oil (0·8 g.). Distillation under reduced pressure gave 2 : 5-bischloromethyltetrahydrofuran (0·5 g., 34%), b. p. (bath temp.) 120—126°/15 mm., n_D^{15} 1·4855 (Found: C, 42·7; H, 6·1; Cl, 43·8. Calc. for $C_6H_{10}OCl_2$: C, 42·6; H, 5·9; Cl, 42·0). Newth and Wiggins (*loc. cit.*) give b. p. (bath temp.) 130°/15 mm., n_D^{15} 1·4540.

Action of Sodium Methoxide on 1 : 2-5 : 6-*Diepoxyhexane.*—Sodium (2 g.) was dissolved in absolute methyl alcohol (40 c.c.) and diepoxyhexane (1·5 g.) was added. The solution was heated under reflux on the water-bath for 6 hours, diluted with water (100 c.c.), and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$) and evaporated to a liquid residue (1·1 g.), distillation of which under reduced pressure gave 5-*hydroxymethyl-2-methoxymethyltetrahydrofuran* as a colourless oil (0·7 g., 36%), b. p. (bath temp.) 159—164°/15 mm., n_D^{25} 1·4511 (Found: C, 56·9; H, 9·6; OMe, 22·2; OH, 11·4. $C_7H_{14}O_3$ requires C, 57·5; H, 9·6; OMe, 21·2; OH, 11·6%).

Methylation of 5-*Hydroxymethyl-2-methoxymethyltetrahydrofuran.*—The monomethoxy-compound (0·39 g.) was heated overnight under gentle reflux with methyl iodide (10 c.c.) and dry silver oxide (1 g.). The methyl iodide was then evaporated and the residue extracted four times with boiling chloroform. The extract was dried ($MgSO_4$) and evaporated to an oil, which was re-subjected to the methyl iodide–silver oxide treatment. This process was repeated three times. The final oily product (0·31 g.) was distilled under reduced pressure giving 2 : 5-*bismethoxymethyltetrahydrofuran* as a colourless, mobile liquid (0·11 g.), b. p. (bath temp.) 90—95°/12 mm., 160—165°/250 mm., n_D^{15} 1·4370 (Found: OMe, 38·0. $C_8H_{16}O_3$ requires OMe, 38·7%).

Methylation of 2 : 5-*Bishydroxymethyltetrahydrofuran.*—The bishydroxy-compound (0·52 g.) (Haworth, Jones, and Wiggins, *J.*, 1945, 1) was heated under gentle reflux with methyl iodide (10 c.c.) and dry silver oxide (1 g.) for 16 hours. The product was isolated as in the preceding experiment; distillation of the crude material (0·63 g.) gave 2 : 5-bismethoxymethyltetrahydrofuran as a colourless, mobile oil, b. p. (bath temp.) 90—95°/12 mm., n_D^{25} 1·4360 (Found: C, 59·2; H, 9·8; OMe, 38·9. Calc. for $C_8H_{16}O_3$: C, 60·0; H, 10·0; OMe, 38·7%).

Action of Ammonia on 1 : 2-5 : 6-*Diepoxyhexane.*—Diepoxyhexane (2·0 g.) was heated with dry methyl alcoholic ammonia (400 c.c.; saturated at 0°) in an autoclave at 120° for 40 hours. The solution was evaporated to a syrup (2·5 g.) which on distillation gave the ring scission product (*C*) as a colourless, highly viscous syrup (1·5 g., 63%), b. p. (bath temp.) 132—138°/0·04 mm., n_D^{22} 1·5161, believed to be 5-*hydroxy*-2-*hydroxymethylpiperidine* (Found: C, 55·5; H, 10·0; N, 10·6. $C_6H_{13}O_2N$ requires C, 55·0; H, 9·9; N, 10·7%). The compound was freely soluble in water giving a strongly alkaline solution.

Acetylation of Compound (*C*) *in Pyridine Solution.*—The material (0·60 g.) was dissolved in dry pyridine (10 c.c.) and acetic anhydride (3 c.c.) added. The solution was kept at room temperature for 12 hours, then at 30° for a further 36 hours; thereafter it was poured into water and extracted with chloroform. The extract was washed successively with dilute sulphuric acid, sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), and evaporated to a syrupy residue (0·89 g.). This was distilled under reduced pressure, giving the *triacetyl* derivative as a colourless, viscous syrup (0·82 g., 70%), b. p. (bath temp.) 159—162°/0·05 mm., n_D^{22} 1·4815 (Found: C, 56·1; H, 7·3; N, 5·5; *O*-Ac, 32·8. $C_{12}H_{19}O_5N$ requires C, 56·0; H, 7·4; N, 5·5; *O*-Ac, 33·4%).

Oxidation of Compound (*C*) *with Sodium Periodate.*—The syrup (*C*) (0·0520 g.) was treated with an excess (about 6 equivs.) of a standard solution of sodium metaperiodate in water. The reaction was followed by the periodical withdrawal of 1 c.c. portions of the reaction mixture, each being added to a solution of potassium iodide (about 1 g.) and sodium hydrogen carbonate (about 0·5 g.) in water (10 c.c.) and the liberated iodine titrated with 0·01N-sodium arsenite solution (see Fig. 2).

Action of Nitrous Acid on the Compound (*C*).—The syrup (*C*) (0·063 g.) was dissolved in water (3 c.c.), acidified (Congo-red) with hydrochloric acid and cooled to 0°. A solution of sodium nitrite (0·05 g.) in water (2 c.c.), also at 0°, was added; no evolution of gas took place. The mixture was allowed to attain room temperature and was kept thereat for 20 hours; it was then evaporated to dryness repeatedly with water until the residue had no action on moist starch–iodide paper. The residue was extracted several times with boiling ethyl acetate and the combined extracts evaporated. A residual brown syrup was obtained which gave a positive reaction to the Liebermann test for a nitroso-compound; the product was therefore the *N*-nitroso-derivative of (*C*).

Treatment of (*C*) *with Toluene-*p*-sulphonyl Chloride.*—The syrup (*C*) (0·10 g.) was dissolved in dry pyridine (5 c.c.) and toluene-*p*-sulphonyl chloride (0·7 g.) added at 0°. After being kept at 30° for 48 hours, the solution was poured into water and extracted with chloroform. The extract was washed successively with dilute sulphuric acid, sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), and evaporated to a very viscous syrup (0·10 g.), which formed a brittle glass when cold but showed no tendency to crystallise on prolonged keeping. The product contained sulphur, was neutral to phenolphthalein in aqueous alcoholic solution, and was probably the tritoluene-*p*-sulphonyl derivative of (*C*) (Found: C, 55·9; H, 4·9. Calc. for $C_{31}H_{31}O_9NS_3$: C, 54·7; H, 5·2%).

*Action of Sodium Iodide on the Toluene-*p*-sulphonyl Derivative of* (*C*).—The compound (0·149 g.) was heated with dry sodium iodide (0·5 g.) and dry acetone (10 c.c.) in a sealed tube at 100—110° for 8 hours. Sodium toluene-*p*-sulphonate (1·2 equivs.) was obtained; evaporation of the acetone filtrate and extraction of the residue with water gave an insoluble material containing nitrogen, sulphur, and iodine.

Acetylation of Compound (*C*) *in Methyl Alcohol Solution.*—The syrup (*C*) (0·70 g.) was dissolved in absolute methyl alcohol (10 c.c.) and acetic anhydride (1 c.c.) added. The solution was kept at room temperature for 3 days, then evaporated in a vacuum over moist potassium hydroxide to a viscous syrup (0·63 g.); this product was distilled under reduced pressure and gave the *N-acetyl* derivative as a colourless viscous syrup, b. p. (bath temp.) 178—184°/0·05 mm., n_D^{22} 1·5128 (Found: C, 56·3; H, 8·95; N, 7·8. $C_8H_{15}O_4N$ requires C, 55·5; H, 8·7; N, 8·1%). The derivative was freely soluble in water but the solution exhibited only a very faintly alkaline reaction, indicating that acetylation of the nitrogen atom had occurred.

*Treatment of the N-Acetyl Derivative with Toluene-*p*-sulphonyl Chloride.*—The acetyl compound (0·14 g.) was treated with pyridine and toluene-*p*-sulphonyl chloride, as described for the syrup (*C*) (above). The syrupy product (0·21 g.) which contained sulphur, partly crystallised after prolonged storage. The resultant *ditoluene-*p*-sulphonyl N-acetyl* derivative of (*C*) (0·013 g.) was separated by filtration; it recrystallised from alcohol in clusters of needles, m. p. 135—136·5° (Found: C, 54·8; H, 5·7; N, 3·0. $C_{22}H_{25}O_8NS_2$ requires C, 54·9; H, 5·6; N, 2·9%).

*Action of Sodium Iodide on the Ditoluene-*p*-sulphonyl N-Acetyl Derivative of* (*C*).—This experiment was carried out on the original syrup before separation of the crystalline matter. The syrup (0·066 g.) when treated with dry sodium iodide (0·1 g.) and dry acetone (10 c.c.) gave sodium toluene-*p*-sulphonate (0·029 g., 1·07 equivs.). The acetone mother liquors were evaporated to dryness, extracted with water, and the insoluble matter taken up in chloroform. After being washed with water and dried ($MgSO_4$) the chloroform solution was evaporated to a syrupy residue (0·05 g.) which was found to contain both iodine and sulphur, confirming the replacement of only one toluene-*p*-sulphonyloxy-group.

*Toluene-*p*-sulphonpiperidide.*—Piperidine (0·85 g.) was dissolved in 10% sodium hydroxide solution (20 c.c.), powdered toluene-*p*-sulphonyl chloride (2·1 g.) was added, and the mixture was shaken vigorously for 20 minutes, the reaction being started by warming on the water-bath. The solid derivative was collected, washed with water and recrystallised from alcohol; it formed stout needles (1·6 g.), m. p. 95—96° (Staudinger and Schneider, *Ber.*, 1923, **56**, 711, record m. p. 98—99° for toluene-*p*-sulphonpiperidide.

*Treatment of Toluene-*p*-sulphonpiperidide with Sodium Iodide.*—The toluene-*p*-sulphonyl derivative was heated with dry sodium iodide and dry acetone; no sodium toluene-*p*-sulphonate was formed.

Action of Lithium Aluminium Hydride on 1 : 2-5 : 6-*Diepoxyhexane.*—Lithium aluminium hydride was prepared essentially according to the method of Finholt, Bond, and Schlesinger (*J. Amer. Chem. Soc.*, 1947, **69**, 1200); the following experiment was based on Nystrom and Brown's general procedure (*loc. cit.*).

To a solution of lithium aluminium hydride (0·5 g.) in ether (20 c.c.) a solution of diepoxyhexane

(0·5 g.) in dry ether (20 c.c.) was added slowly, with stirring. The warm mixture was gently refluxed on the water-bath with continuous stirring for ½ hour. A further addition of lithium aluminium hydride (0·25 g.) in ether (10 c.c.) was then made and the mixture heated under reflux for 1 hour. The product was poured into ice-water acidified with sulphuric acid, the ether layer separated, and the aqueous layer extracted with more ether. The combined ethereal solutions were washed with sodium hydrogen carbonate solution and with water, dried ($MgSO_4$), and evaporated; the residual syrup weighed only 11 mg. The aqueous residues was therefore neutralised with sodium carbonate and evaporated to dryness under reduced pressure; the solid residue was extracted several times with ether under reflux, and the combined extracts dried ($MgSO_4$) and evaporated to a colourless viscous syrup (*D*) (0·33 g.), n_D^{20} 1·4480.

Duden and Lemme (*Ber.*, 1902, **35**, 1335) record hexane-2 : 5-diol as having n_D^{20} 1·4475.

Treatment of (*D*) *with Toluene-p-sulphonyl Chloride.*—The syrup (*D*) (0·08 g.) was dissolved in dry pyridine (2 c.c.) and toluene-*p*-sulphonyl chloride (0·4 g.) added at 0°. After being kept overnight at 20° the product was poured into water, and the solid derivative (0·09 g.) was collected and fractionally crystallised from alcohol, giving an initial fraction (*E*), prisms, m. p. 112·5—114°, and a final fraction (*F*), prisms, m. p. 71—74°.

Preparation of Hexane-2 : 5-diol from Acetonylacetone.—The following experiment is a modification of the method of Hill and Adkins (*J. Amer. Chem. Soc.*, 1938, **60**, 1033).

Acetonylacetone (10 g.) was diluted with alcohol (20 c.c.) and hydrogenated at 200—210° under 200 atmospheres pressure, in the presence of copper chromite catalyst (2 g.) (Lazier and Arnold, *Org. Synth.*, Coll. Vol. II, p. 142), for 2 hours. After filtration the solution was evaporated under reduced pressure giving hexane-2 : 5-diol as a viscous syrup (9 g.), n_D^{20} 1·4494.

Treatment of Hexane-2 : 5-diol with Toluene-p-sulphonyl Chloride.—Hexanediol (0·20 g.) was treated in dry pyridine (5 c.c.) with toluene-*p*-sulphonyl chloride (1·0 g.). The solid derivative (0·25 g.) was fractionally crystallised from dilute alcoholic solution, giving two forms of *hexane-2 : 5-diol ditoluene-p-sulphonate*: the first fraction formed prisms, m. p. 113—114°, undepressed on admixture with fraction (*E*) (Found: C, 56·7; H, 6·4. $C_{20}H_{26}O_6S_2$ requires C, 56·4; H, 6·1%); the final fraction also separated as prisms, m. p. 74—76°, not appreciably depressed on admixture with fraction (*F*) (Found: C, 56·2; H, 6·0%). The m. p. of the final fraction was also undepressed on admixture with the hexane-2 : 5-diol ditoluene-*p*-sulphonate, m. p. 74—77°, prepared by Newth and Wiggins (unpublished work) by acetolysis of 2 : 5-dimethyltetrahydrofuran.

Action of Lithium Aluminium Hydride on **3** : 4-iso*Propylidene* **1** : 2·5 : 6-*Dianhydromannitol.*—To a stirred solution of lithium aluminium hydride (1·2 g.) in dry ether (30 c.c.) *iso*propylidene dianhydromannitol (0·5 g.) dissolved in dry ether (20 c.c.) was added, and the mixture was gently refluxed for 2½ hours. An hour later it was poured into ice-water acidified with sulphuric acid, the ether layer was separated, the aqueous layer extracted with more ether, and the combined ethereal extracts were washed with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and evaporated under reduced pressure. The solid residue (0·21 g.) was recrystallised from light petroleum (40—60°) giving **3** : 4-iso*propylidene* **1** : 6-*dideoxymannitol* as long, prismatic needles, m. p. 90·5—91·5°, $[\alpha]_D^{20}$ −3·9° (*c*, 0·51; in chloroform) (Found: C, 56·4; H, 9·4. $C_9H_{18}O_4$ requires C, 56·8; H, 9·5%).

Hydrolysis of **3** : 4-iso*Propylidene* **1** : 6-*Dideoxymannitol.*—**3** : 4-*iso*Propylidene dideoxymannitol (0·1 g.) was heated with 0·1*N*-sulphuric acid (25 c.c.) at 70° for 1 hour. The solution was neutralised with barium carbonate, the whole was evaporated to dryness, and the residue was extracted with boiling ethyl acetate. Evaporation of the extract gave a crystalline residue (0·05 g.) which on recrystallisation from ethyl acetate yielded **1** : 6-dideoxymannitol in prisms, m. p. 142—144°, $[\alpha]_D^{20}$ −20·9° (*c*, 0·76; in water) (Found: C, 48·2; H, 9·4. Calc. for $C_6H_{14}O_4$: C, 48·0; H, 9·3%). The product gave a positive iodoform reaction, indicating the presence of the $CH_3{\cdot}CH(OH){\cdot}$ group. The m. p. was not depressed on admixture with an authentic specimen prepared by Wiggins's method (*Nature*, 1949, **164**, 672). Micheel (*loc. cit.*) records m. p. 148°, $[\alpha]_D^{20}$ −17·6° (in chloroform) for **1** : 6-dideoxymannitol.

Action of Methylmagnesium Iodide on **1** : 2·5 : 6-*Diepoxyhexane.*—A solution of methylmagnesium iodide was prepared from magnesium (2·4 g., 2·4 mols.), methyl iodide (6·0 c.c., 2·4 mols.), and ether (30 c.c.). A solution of diepoxyhexane (4·4 g., 1 mol.) in dry ether (30 c.c.) was added dropwise with agitation at room temperature. Ether (10 c.c.) was then added and the reaction completed by gentle refluxing on the water-bath for 2½ hours. The mixture was poured into ice-water (300 c.c.) acidified with sulphuric acid, and the ether allowed to evaporate. The solid product (7·3 g.) was exhaustively extracted with ether under reflux, and the insoluble residue recrystallised from hot water, giving **1** : 6-*di-iodo*-**2** : 5-*dihydroxyhexane* as colourless plates (0·4 g.), m. p. 116—117° (Found: C, 19·6; H, 3·5; I, 70·1. $C_6H_{12}O_2I_2$ requires C, 19·5; H, 3·2; I, 68·7%). The ether extract on evaporation gave a solid residue which was recrystallised from hot water containing a little alcohol; the isomeric **1** : 6-*di-iodo*-**2** : 5-*dihydroxyhexane* was obtained as colourless prismatic needles (4·5 g.), m. p. 94—95° (Found: C, 19·8; H, 3·1; I, 68·8%). The aqueous filtrate from the reaction mixture was extracted with ether; evaporation of the extract gave a solid which on recrystallisation yielded a further quantity (0·3 g.) of the lower-melting iodo-compound. The m. p. of a mixture of the two isomers was 95—110°.

Action of Methylmagnesium Iodide on **3** : 4-iso*Propylidene* **1** : 2·5 : 6-*Dianhydromannitol.*—To an agitated solution of methylmagnesium iodide [prepared from magnesium (1·2 g., 2·4 mols.), methyl iodide (3 c.c., 2·4 mols.), and dry ether (20 c.c.)] a solution of *iso*propylidene dianhydromannitol (3·7 g., 1 mol.) in dry ether (20 c.c.) was added slowly at room temperature. The mixture was heated under reflux on the water-bath for 3 hours, and then poured into ice-water (300 c.c.) acidified with sulphuric acid. The ether layer was separated and the aqueous layer extracted with ether; the combined ether solutions were washed with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and evaporated. The resultant syrupy residue (7·5 g.) subsequently almost completely crystallised; recrystallisation from light petroleum (100—120°) gave **1** : 6-*di-iodo* **3** : 4-iso*propylidene* **1** : 6-*dideoxymannitol* as long colourless needles (4·9 g., 54%), m. p. 84° (Found: C, 24·9; H, 3·7; I, 57·1. $C_9H_{16}O_4I_2$ requires C, 24·4; H, 3·6; I, 57·5%).

Hydrolysis of 1 : 6-*Di-iodo* 3 : 4-iso*Propylidene* 1 : 6-*Dideoxymannitol*.—The *iso*propylidene compound (0·15 g.) was boiled with hydrochloric acid (10 c.c.; 2%) until all the oily material had dissolved. On cooling, 1 : 6-di-iodo 1 : 6-dideoxymannitol was deposited as pale yellow plates (0·09 g.), m. p. 165—166° (decomp.). Wiggins (*J.*, 1946, 384) records m. p. 165—167° (decomp.).

Methylenation of 1 : 6-*Di-iodo* 1 : 6-*Dideoxymannitol*.—Di-iodo dideoxymannitol was suspended in approximately twenty times its weight of 40% formalin, and hydrogen chloride passed in at 0° until the solution was saturated. After 2 days at 0° the mixture was diluted with water and the solid collected; recrystallisation from alcohol gave 1 : 6-di-iodo 2 : 4-3 : 5-dimethylene 1 : 6-dideoxymannitol in prisms, m. p. 192—193·5° alone or in admixture with an authentic specimen (Wiggins, *J.*, 1946, 384).

Treatment of 1 : 6-*Di-iodo*-2 : 5-*dihydroxyhexane, m. p.* 94—95°, *with Silver Acetate*.—(i) *In aqueous alcoholic solution*. A solution of silver acetate (1·5 g., 2·2 mols.) in hot water (30 c.c.) was added to the iodo-compound (1·53 g.) in water (25 c.c.) and alcohol (25 c.c.). Silver iodide was immediately precipitated; the reaction was completed by heating under reflux for 3 hours, and the yield of silver iodide was then quantitative. The combined filtrate and washings from the removal of the iodide were evaporated under reduced pressure giving a colourless syrup (0·73 g.), which was acetylated by use of acetic anhydride (4 c.c.) and dry pyridine (20 c.c.). The syrupy product (0·62 g.) was distilled giving 2 : 5-bisacetoxymethyltetrahydrofuran as a colourless, somewhat viscous liquid (0·36 g.), b. p. 158—164°/15 mm., n_D^{20} 1·4511 (Found: C, 55·6; H, 7·45; *O*-Ac, 39·3. Calc. for $C_{12}H_{18}O_5$: C, 55·6; H, 7·4; *O*-Ac, 39·8%). Haworth, Jones, and Wiggins (*loc. cit.*) record b. p. (bath temp.) 115°/0·015 mm., n_D 1·4515.

The acetyl compound (0·09 g.) was hydrolysed by heating it with 0·1*N*-sodium hydroxide solution (25 c.c.) at 90° for 3 hours. The solution was neutralised with hydrochloric acid and evaporated to dryness. Boiling-chloroform extraction of the residue gave a syrup (0·04 g.), which was then treated with toluene-*p*-sulphonyl chloride (0·12 g.) in dry pyridine (5 c.c.) at 0°. 2 : 5-Bishydroxymethyltetrahydrofuran ditoluene-*p*-sulphonate (0·03 g.) was obtained as needles (from alcohol), m. p. 111—115° undepressed on admixture with a specimen obtained by direct hydrolysis of diepoxyhexane.

(ii) *In absolute alcoholic solution*. Finely powdered, dry silver acetate (2·0 g., 3 mols.) was added to a solution of the iodo-compound (1·5 g.) in absolute alcohol (100 c.c.) and the mixture was heated under reflux on the water bath for 4 hours, silver iodide was filtered off and the filtrate was evaporated to about 15 c.c.; a strong odour of acetic acid was noticed. The residue was diluted with chloroform, washed with sodium carbonate solution and with water, dried ($MgSO_4$), and evaporated to an oil which on distillation gave 1 : 2·5 : 6-diepoxyhexane (0·16 g., 35%), b. p. (bath temp.) 125—129°/50 mm., n_D^{19} 1·4410.

The product (0·11 g.) was boiled with water (10 c.c.) for 7 hours, and the solution evaporated to a syrup (0·13 g.) which was dried by evaporation with benzene. The syrup was treated with toluene-*p*-sulphonyl chloride (0·32 g.) in dry pyridine (5 c.c.) giving 2 : 5-bishydroxymethyltetrahydrofuran ditoluene-*p*-sulphonate in needles (from alcohol), m. p. 109—113° not depressed on admixture with a specimen obtained from authentic diepoxyhexane.

Action of Silver Acetate on 1 : 6-*Di-iodo* 3 : 4-iso*Propylidene* 1 : 6-*Dideoxymannitol*.—The iodo-compound (1·2 g.) was heated with absolute alcohol (100 c.c.) and dry, finely powdered silver acetate (1·1 g.) under vigorous reflux for 3 hours. A further quantity (0·8 g.) of silver acetate was added and the mixture heated for 1½ hours. The silver iodide was filtered off and the filtrate, which possessed a strong odour of acetic acid, concentrated to a small bulk; chloroform was added, the solution was washed with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and evaporated. Distillation of the syrupy residue (0·48 g.) afforded 3 : 4-*iso*propylidene 1 : 2·5 : 6-dianhydromannitol (0·34 g., 67%), b. p. (bath temp.) 138—143°/12 mm., n_D^{20} 1·4530, $[\alpha]_D$ zero (in chloroform) (Found: C, 58·3; H, 7·8. Calc. for $C_9H_{14}O_4$: C, 58·1; H, 7·5%). Hydrolysis of the product with dilute acid gave acetone (detected by the iodoform reaction) and mannitol, m. p. 162—165°.

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325. *The Polarographic Reduction of Some Heterocyclic Molecules. Part II. Coumarin and Certain Derivatives thereof.*

By A. J. HARLE and L. E. LYONS.

The polarographic behaviour and the absorption spectra of coumarin indicate that at pH >11·2 it exists entirely in the lactone form and at pH <6·8 entirely as coumarinic acid, both forms being present at intermediate pH. The reduction leads to *meso*- and racemic forms of tetrahydrodi-4-coumarinyl.

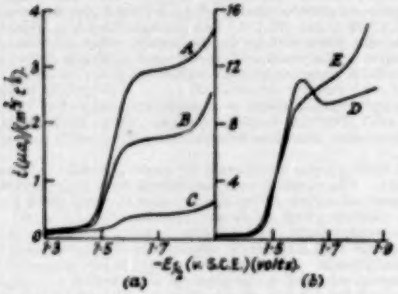
COUMARIN is reported to be reduced in several ways. Zinc dust in alkaline solution gives two dicoumarins (Fries and Fickewirth, *Annalen*, 1908, **362**, 30); sodium amalgam in water gives melilotic acid (Zwenger, *Annalen*, Suppl., 1872, **8**, 32), and in alcohol gives hydrocoumaric acid. Dyson (*J.*, 1887, **51**, 61) studied various reductions but both his and Fries and Fickewirth's conclusions have been questioned by Asahini and Fujita (*J. Pharm. Soc. Japan*, 1919, **444**, 97). The present paper reports the first study of the polarographic reduction of the coumarin nucleus and gives a method which can be used to determine small amounts of coumarins.

The observed polarographic behaviour was simple in that for any pH where reduction

occurred there was a single wave, the half-wave potential, $E_{\frac{1}{2}}$, of which was independent of pH. Maxima, which generally were not observed, appeared at a concentration of 0·005M. (see Fig. 1*b*) and could be removed by gelatin. The wave-height for a given concentration varied with pH as shown in Fig. 1*a*. Below pH 4 no wave was obtained because of the overlying hydrogen discharge.

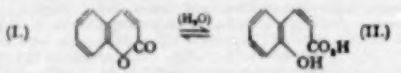
FIG. 1.

Polarographic reduction of coumarin.



Curve A: *pH* 6·62; $c = 1{\cdot}5 \times 10^{-4}$M.
B: *pH* 9·46; $c = 1{\cdot}5 \times 10^{-4}$M.
C: *pH* 10·20; $c = 1{\cdot}5 \times 10^{-4}$M.
D: *without gelatin*; *pH* 6·45; $c = 5 \times 10^{-4}$M.
E: *with 3 drops of 1% gelatin*; *pH* 6·45; $c = 5 \times 10^{-4}$M.

The ultra-violet absorption spectra of coumarin in aqueous buffers at a strength of $1{\cdot}5 \times 10^{-4}$M. are shown in Fig. 2. It is seen that there is a gradual change in the character of the absorption from that at pH 7·56 [$\lambda_{max.}$ = (i) 310, (ii) 278 mμ.; $\epsilon_{max.}$ (i) 6000, (ii) 10,500] to that at pH 12·18 [$\lambda_{max.}$ (i) 330, (ii) 226 mμ.; $\epsilon_{max.}$ (i) 4900, (ii) 13,400]. Both the polarographic and the spectroscopic results are explicable on the assumption of a pH-variable interchange between the lactone (I) and the coumarinic acid (II) form of coumarin.



If the optical densities at the two maxima are plotted against pH (Fig. 3), a marked change in the character of the absorption is seen around pH 9·8. This pH agrees with that (9·3—10·3) at which the polarographic wave-height decreases markedly. Hence it is concluded that the lactone (I), which is from chemical evidence the stable form in acid media, is reducible over the range of potentials studied but that the acid (II) is not reducible over that range; and also that (I) is present to a negligible extent above pH 11·2 and (II) to a negligible extent below pH 6·8. For pH between 6·8 and 11·2 the polarographically estimated proportions of (I) and (II) are shown in Fig. 4 for 25° and 35°. Qualitatively similar figures may be estimated spectroscopically but these are in error owing to the impossibility of finding wave-lengths where the absorption is due exclusively either to (I) or to (II). By use of 240 mμ. to measure (II) and 280 mμ. to measure (I), the curve marked *Sp.* in Fig. 4 was obtained, on the assumption that no lactone is present at pH 11.

The effect of temperature on the relative amounts of (I) and (II) is not great. The pH at which most of the molecules change from (I) to (II) is similar at 35° and 25°, the slight difference observed being of the order of the experimental error, but it is seen that the percentage of (I) is reduced more rapidly with rising pH at 35° than at 25°.

The current at the top of the wave at pH 6·45 (at 25°) is controlled by the diffusion to the surface of the mercury drop, as i_d is proportional to the concentration in the bulk (Fig. 5). It is therefore possible to use these conditions for the quantitative determination of coumarin in small amounts, except in solutions containing a great excess of more easily reducible substances. The effect of temperature on the diffusion current is shown by the following

FIG. 2.

Absorption spectra of coumarin at pH stated.

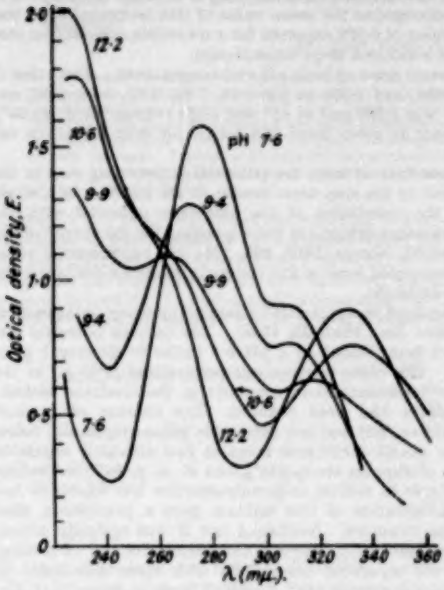


FIG. 3.

Dependence of the optical densities at absorption maxima (for coumarin) on pH.

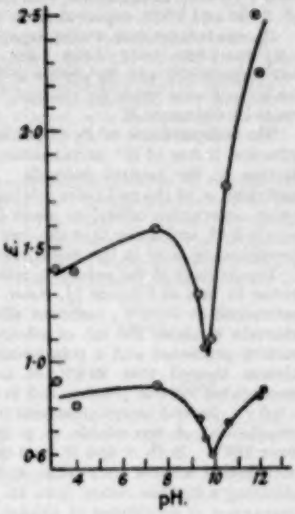


FIG. 4.

Percentage of lactone form (I) present in coumarin solutions.

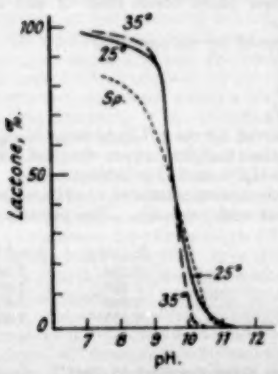
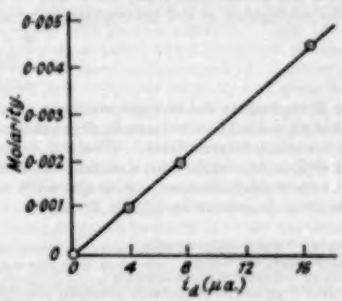


FIG. 5.

Relation of i_d to molarity, for coumarin.



values (μa.) at pH 6·65: 25°, 4·92; 35°, 5·48; 45°, 6·58; these results are attributable to the increase in diffusion coefficient, D, with temperature, i_d varying as $D^{\frac{1}{2}}$ according to the Ilkovic equation, $i_d = 605\ nCD^{\frac{1}{2}}m^{\frac{2}{3}}t^{\frac{1}{6}}$, the symbols having the usual meaning quoted in Part I.

The number, n, of electrons concerned in the reduction process may be calculated, assuming

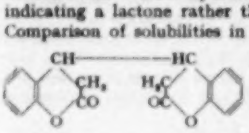
a value of $0{\cdot}8 \times 10^{-6}$ cm.^{2} sec.$^{-1}$ for D (by taking the value for quinaldic acid in the absence of other information). A value of 1·02, *viz.*, 1, was obtained for n.

Evidence to support this value of n was obtained from the reciprocal slopes of the plots of $\log i/(i_d - i)$ against E. For several polarograms the mean value of this reciprocal slope was 0·062 ($\pm$0·010), in agreement with the value of 0·059 expected for a reversible one-electron step (cf. 0·030 and 0·020, expected for 2- and 3-electron steps respectively).

$E_{\frac{1}{2}}$ was independent within experimental error of both pH and temperature. The value of $-E_{\frac{1}{2}}$ was 1·529, 1·551, 1·528, 1·523, 1·526, and 1·534 at pH 6·82, 7·63, 9·31, 9·46, 9·66, and 9·89 respectively, and for pH 6·6 at 35° was 1·526 and at 45° was 1·530 (versus S.C.E. at 25°). Corrections were made for residual current at every point and for the iR drop across the cell due to its resistance R.

The independence of $E_{\frac{1}{2}}$ of pH means that at least the potential-determining step in the reduction is free of H^+ participation, and so the step must consist in the addition of a single electron to the neutral molecule. If the correlation of the half-wave potential with the coefficient, a, of the molecular orbital resonance integral in the expression for the energy of the lowest unoccupied orbital be made (Maccoll, *Nature*, 1949, **163**, 178), the experimental value for a is 0·22, indicating that the first unoccupied level in the coumarin molecule lies below the corresponding level in the naphthalene molecule.

The product of the reduction was obtained in appreciable quantity by using an apparatus similar to that of Lingane (*J. Amer. Chem. Soc.*, 1943, **65**, 1348). The cathode potential was maintained at $-1{\cdot}7$ v., sufficient alcohol being added to a pH 6·8 buffer to dissolve 1 g. of coumarin in about 200 ml. of solution. The white product was precipitated (0·75 g.) as the reaction proceeded and a polarographic determination of coumarin in the resultant cathode solution showed that 99·8% of coumarin had been reduced. The amount of product unaccounted for was possibly still in solution, but was not detectable polarographically below $-2{\cdot}0$ v. Several recrystallisations from glacial acetic acid revealed two difficultly separable components: *A*, less soluble, m. p. 280° (darkening above 235°), and *B*, m. p. 247° (darkening above 220°). Both *A* and *B* were insoluble in sodium carbonate solution but soluble in hot concentrated sodium hydroxide, and acidification of this solution gave a precipitate, thus indicating a lactone rather than an acid structure. Neither *A* nor *B* was optically active. Comparison of solubilities in alcohol, benzene, ether, acetone, and chloroform and of melting points of the separated compounds with those mentioned in the literature suggested that *A* and *B* were isomers $C_{18}H_{14}O_4$, *tetrahydrodi-4-coumarinyl* (Found, *A*: C, 72·4; H, 4·7; *B*: C, 72·9; H, 4·9. $C_{18}H_{14}O_4$ requires C, 73·5; H, 4·8%).



According to Asahini and Fujita (*loc. cit.*) two coumarin nuclei are united at position 4, although there is some doubt about this. *A* and *B* are assigned the annexed formula (*meso*- and racemic forms).

The mechanism of the polarographic reduction suggested by the results is:

$$R + e \longrightarrow R^{\cdot -} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$R^{\cdot -} (+H^+) \longrightarrow RH^{\cdot} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$2RH^{\cdot} \longrightarrow R_2H_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where R represents the lactone coumarin. Step 1 is proved by the pH-invariance of $E_{\frac{1}{2}}$, and step 3 is supported by the formula of the product and the fact that isomers are obtained. Step 2 is the necessary intermediate. Whether $R^{\cdot -}$ reacts with H_3O^+ or H_2O is indefinite.

As well as coumarin, four naturally occurring derivatives were examined at pH's where the lactone form predominated. A single wave was given as with coumarin. The polarographic results for a concentration of 2×10^{-3}M. are:

	$-E_{\frac{1}{2}}$ (corr.).	$i_d/m^{\frac{2}{3}}t^{\frac{1}{6}}$.
7-Hydroxy-8-methoxycoumarin	1·594	2·74
7 : 8-Dimethoxycoumarin	1·590	2·60
7-Methoxy-6-dimethylallylcoumarin	1·668	1·84
8-Methoxy-7-geranyloxycoumarin (collinin)	1·577	1·85

Experimental.

The apparatus and buffer solutions used were similar to those described in Part I. Capillary characteristics were (*a*) $m = 1{\cdot}808$ mg. sec.$^{-\frac{1}{2}}$, (*b*) $m = 2{\cdot}583$ mg. sec.$^{-\frac{1}{2}}$. The coumarin was recrystallised four times from aqueous alcohol (m. p. 67·5°). The resistance, R, of the cell was measured by a "Philoscope." The coumarin derivatives were kindly supplied by Mrs. J. Ewing and Mr. F. Anet.

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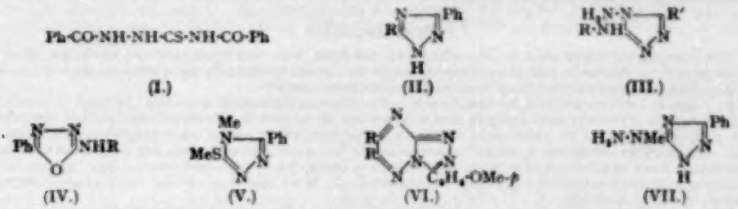
326. *Compounds related to Thiosemicarbazide. Part VI. Further Routes to 4 : 5-Diamino-3-phenyl-4 : 1 : 2-triazole and Related Compounds.*

By Eric Hoggarth.

Alternative routes to 4 : 5-diamino-3-phenyl-4 : 1 : 2-triazole (Part V) have been examined. The compound was found among the products of the reaction of hydrazine with 1 : 4-dibenzoyl-*S*-methyl*iso*thiosemicarbazide and with 1-benzoylthiosemicarbazide and its *S*-methyl ether. Reaction with the last compound was most satisfactory from a preparative point of view, and several compounds substituted in the phenyl nucleus and in the 5-amino-group were prepared in this manner. 1-Benzoyl-*S*-methyl*iso*thiosemicarbazide reacted with methylhydrazine to give a compound, $C_9H_{11}N_5$, whose properties indicated that it was 5-α-methylhydrazino-3-phenyl-1 : 2 : 4-triazole.

In Part V (*J.*, 1950, 614) it was reported that 1 : 4-dibenzoylthiosemicarbazide (I) reacted with hydrazine to give 3-phenyl-1 : 2 : 4-triazole-5-thiol (II; R = SH), benzhydrazide, and 4 : 5-diamino-3-phenyl-4 : 1 : 2-triazole (III; R = H, R′ = Ph). The yield of the last compound was small and alternative routes to it have been sought. On treatment with methyl iodide and sodium hydroxide, 1 : 4-dibenzoylthiosemicarbazide (I) gave the *S-methylisothiosemicarbazide* which when heated behaved like an *S*-methyl ether of a 1-benzoylthiosemicarbazide (Part III,



J., 1949, 1918) in readily losing methanethiol to give 2-benzamido-5-phenyl-1 : 3 : 4-oxadiazole (IV; R = Bz) (also prepared by benzoylating the parent amine). With hydrazine, 1 : 4-dibenzoyl-*S*-methyl*iso*thiosemicarbazide gave some of the diamino-triazole (III; R = H, R′ = Ph) together with benzhydrazide and a *compound* $C_{16}H_{13}ON_5$. The last was not identical with the monobenzoyl derivative of (III; R = H, R′ = Ph) mentioned in Part V (*loc. cit.*) and unlike that benzoyl derivative was not hydrolysed to (III; R = H, R′ = Ph) by acid. The constitution of this compound has not yet been established.

1-Benzoylthiosemicarbazide was heated with an alcoholic solution of hydrazine in a stream of nitrogen, and the effluent gas washed with acidified lead acetate solution. Only 10—15% of the expected lead sulphide (on the basis of complete elimination) was formed, and the reaction products were separated, giving a small amount of 4 : 5-diamino-3-phenyl-4 : 1 : 2-triazole, the remainder consisting of the triazole-thiol (II; R = SH). By this method, 4 : 5-*diamino*-3-p-*methoxyphenyl*- (III; R = H, R′ = *p*-MeO·C$_6$H$_4$) and 4-*amino*-5-*anilino*-3-*phenyl*-4 : 1 : 2-*triazole* (III; R = R′ = Ph) were prepared, the yield in the last case being much higher than with other 1-benzoylthiosemicarbazides examined. Both 1-*p*-chlorobenzoylthiosemicarbazide and 1-benzoyl-4-methylthiosemicarbazide gave a very small amount of hydrogen sulphide and none of the corresponding diamine was isolated. However, all the preceding diamino-triazoles and 4 : 5-*diamino*-3-p-*chlorophenyl*- (III; R = H, R′ = *p*-C$_6$H$_4$Cl) and 4-*amino*-5-*methylamino*-3-*phenyl*-4 : 1 : 2-*triazole* (III; R = Me, R′ = Ph) were prepared by reaction of the corresponding benzoyl-*S*-methyl*iso*thiosemicarbazides with hydrazine, and this is the best preparative method although it is necessary to separate the triazole from two other reaction products, namely, the corresponding benzhydrazides and 2-amino-5-phenyl-1 : 3 : 4-oxadiazoles. The reaction with 1-benzoyl-4 : *S*-dimethyl*iso*thiosemicarbazide was further complicated by the formation of 5-methylthio-3-phenyl-4-methyl-4 : 1 : 2-triazole (V) in addition to the other products. The occurrence of this compound amongst the products of cyclisation of this *S*-methyl*iso*thiosemicarbazide with acids has been reported (Part III, *loc. cit.*). Two new 3-p-*methoxyphenyl*-1 : 2 : 4 : 7 : 9-*penta-azaindenes* (VI; R = Me or Ph) were formed by condensation of (III; R = H, R′ = *p*-MeO·C$_6$H$_4$) with diacetyl and benzil respectively, as described in Part V.

Reaction between 1-benzoyl-*S*-methylisothiosemicarbazide and methylhydrazine gave the amino-oxadiazole (IV; R = H) and a *compound* $C_9H_{11}N_5$. However, this compound cannot be the expected 5-amino-4-methylamino-3-phenyl-4 : 1 : 2-triazole, since it was freely soluble in dilute alkalis, indicating the presence of a hydrogen atom on one of the nitrogen atoms of the triazole ring. It was therefore a 5-methylhydrazino-1 : 2 : 4-triazole and since it formed a *benzylidene* and a *p-methoxybenzylidene* derivative was probably 5-α-methylhydrazino-3-phenyl-1 : 2 : 4-triazole (VII). In a similar experiment using *NN*-dimethylhydrazine, the major product, apart from amino-oxadiazole (IV; R = H) was 5-methylthio-3-phenyl-1 : 2 : 4-triazole (II; R = SMe), the dimethylhydrazine having induced cyclisation of the *S*-methylisothiosemicarbazide in the manner previously noted with other organic bases (Part IV, *J.*, 1950, 612). Only a small amount of the methylthio-triazole was formed in the reaction with methylhydrazine (which resembles, in this, piperidine and, as mentioned below, dimethylamine) and, except for the reaction with 1-benzoyl-4 : *S*-dimethylisothiosemicarbazide noted above, such cyclisations have not been detected with hydrazine. A very small amount of a compound $C_{10}H_{12}N_4$ was isolated from the reaction between 1-benzoyl-*S*-methylisothiosemicarbazide and *NN*-dimethylhydrazine and this proved to be *5-dimethylamino-3-phenyl-1 : 2 : 4-triazole* (II; R = NMe_2) identical with a specimen prepared by treating the thiosemicarbazide with dimethylamine. It is probable that the dimethylhydrazine prepared by reduction of nitrosodimethylamine (*Org. Synth. Coll.*, Vol. II, 211) contained a trace of dimethylamine, which would account for the occurrence of the dimethylamino-triazole.

Experimental.

The compounds mentioned below, which are not new, have been prepared in work described in earlier papers in this series and in each case (though this is not specifically mentioned in the text) mixed melting-point determinations have been made to confirm identity.

1 : 4-*Dibenzoyl-S-methylisothiosemicarbazide*.—The dibenzoylthiosemicarbazide (12·0 g.) in *N*-sodium hydroxide (40 c.c.) was ground finely to give a dispersion of the yellow sodium salt and shaken vigorously with methyl iodide (4·0 c.c.) and alcohol (20 c.c.) until the yellow colour was completely discharged, a little more methyl iodide being added as necessary. The solid was collected, dried in a vacuum, and crystallised from alcohol–ethyl acetate (50 : 50), care being taken to avoid overheating, giving large, colourless, refractive prisms (7·5 g.), m. p. 171° (Found: C, 61·8; H, 5·0; S, 10·5. $C_{18}H_{18}O_2N_3S$ requires C, 61·4; H, 4·8; S, 10·2%).

2-Benzamido-5-phenyl-1 : 3 : 4-oxadiazole (IV; R = Bz).—The above *S*-methylisothiosemicarbazide (1·0 g.) was heated in an oil-bath at 150° for 30 minutes and then cooled and the residue crystallised from alcohol, giving colourless needles (0·5 g.), m. p. 201° not depressed by a specimen prepared by benzoylation of the amino-oxadiazole (Fehrenbach and Stolle, *J. pr. Chem.*, 1929, **122**, 289) (Found: C, 68·2; H, 4·4. Calc. for $C_{15}H_{11}O_2N_3$: C, 67·9; H, 4·2%).

Reaction of 1 : 4-*Dibenzoyl-S-methylisothiosemicarbazide with Hydrazine*.—The *S*-methylisothiosemicarbazide (5·2 g.), alcohol (20 c.c.), and 50% hydrazine hydrate (5·0 c.c.) were refluxed for 12 hours and the solvent was removed under reduced pressure. Water (50 c.c.) was added, followed by concentrated hydrochloric acid, and the insoluble hydrochloride was collected and sucked dry. The filtrates were evaporated to half bulk and then cooled and a further crop of hydrochloride was collected. The united solid (1·7 g.) was rubbed with 10% potassium hydrogen carbonate solution, and the solid *product* collected (1·5 g.; m. p. 180—186°) and crystallised from ethyl acetate, giving small colourless needles (0·75 g.), m. p. 196° (Found: C, 64·3; H, 4·7; N, 24·9. $C_{14}H_{13}ON_5$ requires C, 64·5; H, 4·7; N, 25·1%). The original acid filtrates were concentrated to half bulk, and (with good cooling) treated with 40% potassium hydroxide solution (20 c.c.). The solid was collected (1·2 g.) and crystallised from water, giving colourless plates (0·7 g.) of 4 : 5-diamino-3-phenyl-4 : 1 : 2-triazole, m. p. 223° (Found: C, 55·3; H, 5·4. Calc. for $C_8H_9N_5$: C, 54·9; H, 5·1%). The original alkaline filtrates were made just acid with acetic acid and evaporated under reduced pressure and the dry residue was extracted with chloroform. Evaporation of the dried extracts gave benzhydrazide (1·5 g.) which crystallised from benzene in colourless plates (1·0 g.), m. p. 112° (Found: C, 62·0; H, 6·1. Calc. for $C_7H_8ON_2$: C, 61·8; H, 5·9%).

Reaction of 1-*Benzoylthiosemicarbazide with Hydrazine*.—1-Benzoylthiosemicarbazide (3·9 g.), alcohol (50 c.c.), and 50% hydrazine hydrate (8·0 c.c.) were refluxed in a stream of nitrogen and the effluent gas was washed in acidified lead acetate solution. When evolution of hydrogen sulphide ceased (6 hours) the precipitated lead sulphide was collected in a Gooch crucible, well washed, and dried at 110° (0·71 g.). The reaction liquid was evaporated under reduced pressure, water (100 c.c.) added, and the resultant solution made strongly acid with hydrochloric acid. The precipitate was collected (1·8 g.; m. p. 230—238°) and crystallised from water with a little alcohol (it was necessary to cool the solution slowly and to filter it from a small flocculent precipitate which separated first and appeared to hinder crystallisation), giving colourless needles (0·8 g.) of 3-phenyl-1 : 2 : 4-triazole-5-thiol, m. p. 256—257° (Found: C, 54·1; H, 4·2. Calc. for $C_8H_7N_3S$: C, 54·2; H, 4·0%). The flocculent precipitate afforded on crystallisation a little more of the thiol (0·1 g.; m. p. 256°). The original acid filtrate was evaporated and treated with 10*N*-sodium hydroxide (10 c.c.), and the solid collected (0·5 g.; m. p. 220°) and crystallised from water, giving colourless plates (0·3 g.) of 4 : 5-diamino-3-phenyl-4 : 1 : 2-triazole, m. p. 223° (Found: C, 55·0; H, 5·2%).

The following were obtained in analogous experiments: 4 : 5-*diamino-3-p-methoxyphenyl-* (III; R = H, R′ = *p*-MeO·C_6H_4), colourless glistening plates, m. p. 242°, from water (Found: C, 52·5;

H, 5·8; N, 34·6. $C_9H_{11}ON_5$ requires C, 52·7; H, 5·4; N, 34·1%) [3-*p*-methoxyphenyl-1 : 2 : 4-triazole-5-thiol, colourless needles, m. p. 255°, from aqueous alcohol, was also isolated (Found : C, 51·9; H, 4·4. Calc. for $C_9H_9ON_3S$: C, 52·2; H, 4·35%)], and *4-amino-5-anilino-3-phenyl-4* : 1 : 2-*triazole* (III; R = R′ = Ph), colourless leaflets, m. p. 286°, from 2-ethoxyethanol (Found : C, 67·0; H, 5·5; N, 27·9. $C_{14}H_{13}N_5$ requires C, 66·9; H, 5·2; N, 27·9%) [3 : 4-diphenyl-4 : 1 : 2-triazole-5-thiol, colourless needles, m. p. 290°, from alcohol was also isolated (Found : C, 66·0; H, 4·6. Calc. for $C_{14}H_{11}N_3S$: C, 66·4; H, 4·3%)]. Under the same conditions, 1-benzoyl-4-methylthiosemicarbazide gave only 3-phenyl-4-methyl-4 : 1 : 2-triazole-5-thiol, colourless needles, m. p. 166°, from aqueous alcohol (Found : C, 56·5; H, 4·8. Calc. for $C_9H_9N_3S$: C, 56·5; H, 4·7%), and 1-*p*-chlorobenzoylthiosemicarbazide gave only 3-*p*-chlorophenyl-1 : 2 : 4-triazole-5-thiol, colourless small needles, m. p. 295°, from aqueous alcohol (Found : S, 15·3. Calc. for $C_8H_6N_3ClS$: S, 15·1%). Very little lead sulphide was formed in the second pair of experiments but the amounts of it formed in the first pair were 0·9 g. and 2·6 g. respectively in experiments on the same scale as that with 1-benzoylthiosemicarbazide (0·02 g.-mol.).

Reaction of 1-*Benzoyl-S-methylisothiosemicarbazide with Hydrazine.*—The *S*-methylisothiosemicarbazide (5·1 g.), 50% hydrazine hydrate (9 c.c.), and alcohol (25 c.c.) were set aside for 12 hours and then refluxed for 1 hour. The solvents were evaporated under reduced pressure, the residue was dissolved in water (25 c.c.), and 40% potassium hydroxide solution (15 c.c.) added slowly with good cooling. The solid was collected and washed with a little ice-water. The filtrates were made just acid with acetic acid and benzhydrazide was isolated as previously and crystallised from benzene, giving colourless plates (0·9 g.), m. p. 112° (Found : C, 61·5; H, 5·5%). The solid precipitated by potassium hydroxide was dissolved in water (50 c.c.) and N-hydrochloric acid (20 c.c.), filtered (charcoal), and carefully neutralised with potassium hydrogen carbonate. The precipitate was collected and crystallised from alcohol, giving colourless prisms (0·7 g.) of 2-amino-5-phenyl-1 : 3 : 4-oxadiazole (IV; R = H), m. p. 242—244° (Found : C, 59·7; H, 4·3. Calc. for $C_8H_7ON_3$: C, 59·6; H, 4·3%). The original neutralised solution was concentrated under reduced pressure, and, with strong cooling, 40% potassium hydroxide solution was added. The precipitated 4 : 5-diamino-3-phenyl-4 : 1 : 2-triazole (1·2 g.) was crystallised from water or alcohol, giving large colourless plates (0·9 g.), m. p. 226° (Found : C, 55·1; H, 5·1; N, 40·3%).

4 : 5-*Diamino-3-p-methoxyphenyl-4* : 1 : 2-*triazole* (III; R = H, R′ = *p*-MeO·C_6H_4).—*p*-Methoxybenzoyl-*S*-methylisothiosemicarbazide (4·8 g.) reacted as above, giving *p*-methoxybenzhydrazide, colourless prisms (1·5 g.), m. p. 136° from xylene (Found : C, 57·5; H, 6·0. Calc. for $C_8H_{10}O_2N_2$: C, 57·8; H, 6·0%), 2-amino-5-*p*-methoxyphenyl-1 : 3 : 4-oxadiazole, colourless needles (0·8 g.), m. p. 248—249°, from alcohol (Found : C, 56·9; H, 4·8. Calc. for $C_9H_9O_2N_3$: C, 56·6; H, 4·7%), and the diamine, colourless plates (0·7 g.), m. p. 242°, from water (Found : C, 52·5; H, 5·5; N, 34·5%).

This diamine, by reaction with diacetyl and benzil as described for 4 : 5-diamino-3-phenyl-4 : 1 : 2-triazole (Part V, *loc. cit.*), gave 3-*p*-*methoxyphenyl*-5 : 6-*dimethyl*-1 : 2 : 4 : 7 : 9-*penta-azaindene* (VI; R = Me), yellow needles, m. p. 215°, from alcohol (Found : C, 60·9; H, 5·1. $C_{15}H_{15}ON_5$ requires C, 61·2; H, 5·1%), and the corresponding 5 : 6-*diphenyl* compound (VI; R = Ph), deep yellow needles, m. p. 247°, from alcohol (Found : C, 72·6; H, 4·4. $C_{25}H_{19}ON_5$ requires C, 72·6; H, 4·6%).

4 : 5-*Diamino-3-p-chlorophenyl-4* : 1 : 2-*triazole* (III; R = H, R′ = *p*-C_6H_4Cl).—1-*p*-Chlorobenzoyl-*S*-methylisothiosemicarbazide (12·1 g.), treated as for the benzoyl compound, gave *p*-chlorobenzhydrazide, colourless plates (3·9 g.), m. p. 164° from water (Found : C, 49·1; H, 3·7. Calc. for $C_7H_7ON_2Cl$: C, 49·3; H, 4·1%). The separation using bicarbonate was unsatisfactory in this case and the solid product insoluble in sodium hydroxide was repeatedly extracted with small amounts of hot water, the united filtrates were concentrated, filtered (charcoal), and allowed to crystallise, giving the *diamine* as colourless leaflets (1·4 g.), m. p. 236° (Found : C, 46·0; H, 3·7; N, 33·7. $C_8H_8N_5Cl$ requires C, 45·8; H, 3·8; N, 33·4%). The residue left after extraction with water crystallised from alcohol, giving long yellow needles (0·7 g.) of 2-amino-5-*p*-chlorophenyl-1 : 3 : 4-oxadiazole, m. p. 273—274° (Found : C, 49·1; H, 3·2. Calc. for $C_8H_6ON_3Cl$: C, 49·1; H, 3·1%).

4-*Amino-5-methylamino-3-phenyl-4* : 1 : 2-*triazole* (III; R = Me, R′ = Ph).—1-Benzoyl-4 : *S*-dimethylisothiosemicarbazide (4·6 g.), alcohol (25 c.c.), and 50% hydrazine hydrate (8·0 c.c.) were refluxed together for 6 hours and the solvent was removed under reduced pressure. The residue was treated with water (50 c.c.) and 40% potassium hydroxide solution (10 c.c.), and the solid collected and dried (3·6 g.) (Found : S, 8·1%). The solid was refluxed with benzene (50 c.c.) and light petroleum (b. p. 60—80°; 50 c.c.) and filtered hot from an insoluble residue. This residue was crystallised twice from ethyl acetate, giving colourless glistening leaflets (0·2 g.) of the *diamine*, m. p. 222° (Found : C, 56·3; H, 6·0; N, 37·3. $C_9H_{11}N_5$ requires C, 57·2; H, 5·8; N, 37·0%). The benzene–light petroleum extracts were re-heated, filtered (charcoal), and allowed to crystallise slowly, giving a mixture of large plates and clumps of small needles. The plates were removed as fully as possible by hand (0·5 g.; m. p. 125—128°) and recrystallised from the same solvents, giving large colourless plates (0·3 g.) of 5-methylthio-3-phenyl-4-methyl-4 : 1 : 2-triazole, m. p. 137° (Found : C, 58·2; H, 5·4; S, 15·5. Calc. for $C_{10}H_{11}N_3S$: C, 58·5; H, 5·4; S, 15·6%); the residual crystals were dissolved in the mother-liquor, filtered (charcoal), and allowed to crystallise slowly; the liquor was decanted from the clumps of small needles (0·8 g.; m. p. 150—152°) which were recrystallised from the same solvents, giving colourless needles (0·5 g.) of 2-methylamino-5-phenyl-1 : 3 : 4-oxadiazole, m. p. 153° (Found : C, 61·5; H, 5·0. Calc. for $C_9H_9ON_3$: C, 61·8; H, 5·1%).

4-*Amino-5-anilino-3-phenyl-4* : 1 : 2-*triazole* (III; R = R′ = Ph).—1-Benzoyl-4-phenyl-*S*-methylisothiosemicarbazide (3·2 g.) gave the diamine which crystallised from 2-ethoxyethanol in colourless leaflets (0·25 g.), m. p. 288° (Found : C, 66·6; H, 5·4%), and 2-anilino-5-phenyl-1 : 3 : 4-oxadiazole which crystallised from alcohol in colourless needles (1·7 g.), m. p. 212° (Found : C, 70·5; H, 5·0. Calc. for $C_{14}H_{11}ON_3$: C, 70·8; H, 4·6%). These compounds were separated by extracting the more soluble oxadiazole with alcohol.

Reaction of 1-*Benzoyl-S-methylisothiosemicarbazide with Methylhydrazine.*—The *S*-methylisothiosemicarbazide (8·4 g.), alcohol (25 c.c.), and methylhydrazine (5·0 c.c.) were refluxed together for 12 hours and evaporated under reduced pressure. Water (15 c.c.) was added, and, with strong cooling, 10N-

sodium hydroxide (15 c.c.) added with shaking. The solid was collected, washed with a little N-NaOH, and dried in a vacuum (1·5 g.; m. p. 222—228°). None of the procedures used above for separating a 4 : 5-diamino-4 : 1 : 2-triazole gave an analogous substance and by crystallisation of this material from alcohol, colourless prisms (1·2 g.) of 3-amino-5-phenyl-1 : 3 : 4-oxadiazole, m. p. 242°, were obtained. The original alkaline liquor was made just acid with acetic acid, and the precipitate allowed to harden, collected, washed with water (5·5 g.; m. p. 168—170°) (Found: S, 1·7%), ground with N-hydrochloric acid (20 c.c.) for 2 minutes, and quickly filtered. The extraction was repeated on the residue (0·8 g.) using acid (5 c.c.) and giving an ultimate residue (0·05 g.), which crystallised from aqueous alcohol in colourless plates, m. p. 161—162° (5-methylthio-3-phenyl-1 : 2 : 4-triazole). The acid extracts were neutralised with potassium hydrogen carbonate, giving precipitates (3·0 g., m. p. 178—180°; and 0·5 g., m. p. 180—181°) which were crystallised from aqueous alcohol, giving colourless glistening plates (2·8 g. in all), m. p. 184—185°, of *5-s-methylhydrazino-3-phenyl*-1 : 2 : 4-*triazole* (Found: C, 57·1, 57·2; H, 5·5, 5·6; N, 30·4. $C_9H_{11}N_5$ requires C, 57·1; H, 5·8; N, 37·0%). When this compound (0·5 g.) was refluxed with alcohol (10 c.c.) and benzaldehyde (1·0 c.c.) for 12 hours and evaporated under reduced pressure, crystallisation from aqueous alcohol gave colourless needles (0·5 g.) of the *benzylidene* compound, m. p. 191—192° (Found: C, 69·5; H, 5·6; N, 25·4. $C_{16}H_{15}N_5$ requires C, 69·3; H, 5·4; N, 25·3%). By use of *p*-anisaldehyde (1·0 c.c.) in place of benzaldehyde, the corresponding *p-methoxybenzylidene* compound was obtained as colourless prisms (0·7 g.), m. p. 192—193° (Found: C, 66·3; H, 5·7. $C_{17}H_{17}ON_5$ requires C, 66·45; H, 5·5%).

Reaction of 1-*Benzoyl-S-methylisothiosemicarbazide with* NN-*Dimethylhydrazine*.—The above experiment was repeated using *NN*-dimethylhydrazine (12 c.c.) and gave 2-amino-5-phenyl-1 : 3 : 4-oxadiazole (5·5 g.), m. p. 241—242°. No 4 : 5-diamino-4 : 1 : 2-triazole could be detected. The precipitate (0·8 g.; m. p. 154—156°) (Found: S, 16·4%) obtained from the alkaline mother-liquors by making them just acid with acetic acid was almost pure 5-methylthio-3-phenyl-1 : 2 : 4-triazole and crystallised from aqueous alcohol in colourless shining leaflets (0·6 g.), m. p. 162—163° (Found: S, 16·7. Calc. for $C_9H_9N_3S$: S, 16·75%). The faintly acid mother-liquors were extracted with ether in an automatic apparatus, the solvent was removed, and the residue crystallised twice from benzene–light petroleum (b. p. 60—80°) giving hard, refractive, faintly yellow prisms (0·1 g.), m. p. 203—204° not depressed by admixture with *5-dimethylamino-3-phenyl*-1 : 2 : 4-*triazole* (see below) (Found: C, 64·3; H, 6·3; N, 30·0. $C_{10}H_{13}N_5$ requires C, 63·8; H, 6·4; N, 29·8%).

5-Dimethylamino-3-phenyl-1 : 2 : 4-*triazole* (II; R = NMe_2).—A mixture of 1-benzoyl-*S*-methylisothiosemicarbazide (4·2 g.), alcohol (25 c.c.), and dry dimethylamine (6·0 g.) was heated in a sealed tube at 100° for 12 hours. After the solvent had been removed and the residue made alkaline with N-sodium hydroxide (50 c.c.), 2-amino-5-phenyl-1 : 3 : 4-oxadiazole (0·5 g.), m. p. 241—242°, was isolated in the usual way. The precipitate obtained from the alkaline liquor by neutralising it with acetic acid (3·0 g.; m. p. 185—190°) (Found: S, 2·3%) was rubbed with N-hydrochloric acid (30 c.c.). An almost clear solution was obtained, and then a very sparingly soluble hydrochloride rapidly separated. This was collected, ground once with N-hydrochloric acid, again collected, and washed with a little N-hydrochloric acid. Neutralisation of the filtrates with potassium hydrogen carbonate gave the methylthio-triazole, colourless plates (0·25 g.), m. p. 162—163° from aqueous alcohol (Found: S, 17·1%). The insoluble hydrochloride was dissolved in hot water (80 c.c.), filtered hot, and made just alkaline with potassium hydrogen carbonate, giving the dimethylamino-triazole which crystallised from aqueous alcohol in large, colourless, hard, refractive prisms (2·0 g.), m. p. 207—208° (Found: C, 63·7; H, 6·2%).

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327. *Compounds related to Thiosemicarbazide. Part VII. Benzylthiosemicarbazides.*

By ERIC HOGGARTH and E. H. P. YOUNG.

Examples of 1-, 2-, and 4-benzylthiosemicarbazides have been prepared. These compounds were distinguished by their behaviour towards ferric chloride: 1-benzylthiosemicarbazides gave benzaldehyde thiosemicarbazones, 2-benzylthiosemicarbazide gave benzaldehyde 2-benzylthiosemicarbazone, and 4-benzylthiosemicarbazide gave benzyl *iso*thiocyanate. The last reaction was general for a number of 4- and 2 : 4-substituted thiosemicarbazides.

IT is known that benzaldehyde semicarbazones are reduced by mild reducing agents to 1-benzylsemicarbazides (Kessler and Rupe, *Ber.*, 1912, **45**, 26), and a number of benzaldehyde thiosemicarbazones (I; R = H, *p*-OH, *p*-OMe, *p*-NMe_2 or *p*-SO_2Et) was readily reduced by sodium amalgam to give the corresponding 1-*benzylthiosemicarbazides* (II). The same reaction also proceeded smoothly with the thiosemicarbazones of acetophenone and *p*-methoxyacetophenone, giving the corresponding 1-1′-*phenylethylthiosemicarbazides*. It was noted that the melting point of 1-benzylthiosemicarbazide itself (155°) was the same as that which has been recorded by Cattelain (*Compt. rend.*, 1939, **207**, 799; *Bull. Soc. chim.*, 1940, **7**, 791) for the 2-isomer (III; R = H), and as the method used by this author (isomerisation of the thiocyanate salt of benzylhydrazine by heat) is not unambiguous, attempts were made to repeat this preparation in order to compare the product with that obtained by reduction of the thiosemi-

carbazone. The product obtained by heating the thiocyanate of benzylhydrazine as described in the papers cited was difficult to purify and it was found preferable to heat benzylhydrazine hydrochloride with dry ammonium thiocyanate in absolute alcohol. (Heating under aqueous conditions also gave a product which was difficult to purify.) The melting point of the compound obtained when using alcohol was raised by crystallisation to 171°, but this compound must be the same as that isolated by Cattelain as its benzylidene and *p*-methoxybenzylidene derivatives had the m. p.s recorded by him. By reaction of *p*-methoxybenzylhydrazine with ammonium thiocyanate under similar conditions, the *compound* (III; R = *p*-OMe) was obtained; this was also distinct from the isomer obtained by reduction of *p*-methoxybenzaldehyde thiosemicarbazone. 4-Benzyl- and 4-p-*methoxybenzyl-thiosemicarbazide* (IV; R = H or *p*-OMe) were prepared by a route which has been used for the first of these by Baird, Burns, and Wilson (*J.*, 1927, 2531). When (III; R = H) or (IV; R = H) in dilute acids was shaken with a solution of benzaldehyde in alcohol, the corresponding thiosemicarbazone was at once precipitated. Nothing separated when (II; R = H) was treated in the same way.

$R{\cdot}C_6H_4{\cdot}CH{:}N{\cdot}NH{\cdot}CS{\cdot}NH_2$ (I.)

$R{\cdot}C_6H_4{\cdot}CH_2{\cdot}NH{\cdot}NH{\cdot}CS{\cdot}NH_2$ (II.)

$R{\cdot}C_6H_4{\cdot}CH_2{\cdot}\overset{NH_2}{\underset{|}{N}}{\cdot}CS{\cdot}NH_2$ (III.)

$NH_2{\cdot}NH{\cdot}CS{\cdot}NH{\cdot}CH_2{\cdot}C_6H_4R$ (IV.)

Oxidation of 1-benzylthiosemicarbazides (II; R = H, *p*-OMe, or *p*-SO_2Et) in dilute acetic acid with ferric chloride gave the corresponding thiosemicarbazones. With the first compound, 2-amino-5-phenyl-1 : 3 : 4-thiadiazole (which is known to be formed by the action of mild oxidising agents on benzaldehyde thiosemicarbazone) was also isolated. Oxidation of 2-benzylthiosemicarbazide under the same conditions gave as the main product the benzaldehyde 2-benzylthiosemicarbazone. Presumably this is formed by oxidative breakdown of part of the thiosemicarbazide to benzaldehyde and condensation of this with unchanged thiosemicarbazide, giving the insoluble thiosemicarbazone, which is precipitated. Oxidation of 4-benzylthiosemicarbazide under the same conditions gave benzyl *iso*thiocyanate and this reaction proved to be general for the following 4-substituted thiosemicarbazides (prepared by condensation of appropriate *iso*thiocyanates and hydrazines): 4-ethyl-, 4-iso*propyl*-, 4-iso*butyl*-, 2-*methyl*-4-iso*propyl*- and 4-phenyl-thiosemicarbazide.

Experimental.

1-*Benzylthiosemicarbazide* (II; R = H).—Benzaldehyde thiosemicarbazone (9·0 g.) and alcohol (80%; 400 c.c.) were heated under reflux with good stirring whilst sodium amalgam (11·0 g. of sodium in 20 c.c. of mercury) was added in small pieces during 2 hours. After a further hour the solution was decanted from the residual amalgam which was washed with a little alcohol, and the united alcoholic liquors were diluted with ice and water (300 g.). Acetic acid was added to exact neutrality and the solution set aside at 0° overnight. The crystals (8·5 g.) were collected, washed with water, and crystallised from alcohol, giving 1-*benzylthiosemicarbazide* as colourless needles (6·0 g.), m. p. 154—155° (Found: C, 52·8; H, 6·2; S, 17·4. $C_8H_{11}N_3S$ requires C, 53·0; H, 6·1; S, 17·7%).

The following compounds were obtained in similar experiments: 1-p-*hydroxybenzyl*- (II; R = *p*-OH), large colourless needles, m. p. 180°, from alcohol (Found: C, 49·0; H, 5·5; S, 16·0. $C_8H_{11}ON_3S$ requires C, 48·7; H, 5·6; S, 16·2%), 1-p-*methoxybenzyl*- (II; R = *p*-OMe), large colourless prisms, m. p. 142—143°, from alcohol (Found: C, 51·4; H, 6·4; S, 15·2. $C_9H_{13}ON_3S$ requires C, 51·2; H, 6·2; S, 15·2%), 1-p-*dimethylaminobenzyl*- (II; R = *p*-NMe_2), colourless needles, m. p. 147°, from alcohol (Found: C, 53·6; H, 7·1; S, 14·3. $C_{10}H_{16}N_4S$ requires C, 53·6; H, 7·1; S, 14·3%), 1-p-*ethylsulphonylbenzyl*- (II; R = *p*-SO_2Et), colourless small needles, m. p. 155°, from alcohol (Found: C, 44·3; H, 5·3; S, 23·7. $C_{10}H_{15}O_2N_3S_2$ requires C, 44·0; H, 5·5; S, 23·4%), 1-1′-*phenylethyl*-, colourless leaflets, m. p. 156°, from alcohol (Found: C, 55·3; H, 6·3; S, 16·6. $C_9H_{13}N_3S$ requires C, 55·4; H, 6·7; S, 16·4%), and 1-(1-p-*methoxyphenylethyl*)-*thiosemicarbazide*, colourless glistening leaflets, m. p. 150°, from alcohol (Found: C, 53·4; H, 6·5; S, 14·2. $C_{10}H_{15}ON_3S$ requires C, 53·3; H, 6·7; S, 14·2%).

2-*Benzylthiosemicarbazide* (III; R = H).—(*a*) Freshly distilled benzylhydrazine was dissolved in dry ether, the solution saturated with dry hydrogen chloride, and the dihydrochloride collected, washed with ether, and dried in a vacuum. This dihydrochloride (9·8 g.), dry ammonium thiocyanate (3·8 g.), and absolute alcohol (100 c.c.) were refluxed for 24 hours and then cooled, and the crystals (1·4 g.; m. p. 170°) collected and crystallised from alcohol, giving colourless needles (1·1 g.), m. p. 171° (Found: C, 52·8; H, 6·0; N, 23·0; S, 17·6. Calc. for $C_8H_{11}N_3S$: C, 53·0; H, 6·1; N, 23·2; S, 17·7%).

(*b*) Benzylhydrazine dihydrochloride (19·5 g.) and ammonium thiocyanate (11·2 g.) were dissolved in water (200 c.c.), and the solution was slowly evaporated in a dish during 24 hours. The residue was digested on the steam-bath with water (200 c.c.) for a further 4 hours and then allowed to cool, and the solid collected (6·0 g.; m. p. 150—160°). Several crystallisations from alcohol gave colourless needles (1·0 g.), m. p. 166° not depressed by the compound prepared as in (*a*) (Found: S, 17·8%).

2-Benzylthiosemicarbazide (0·9 g.) in *N*-hydrochloric acid (5·0 c.c.) and alcohol (50 c.c.) was shaken with benzaldehyde (0·6 g.) in a little alcohol. Crystals (0·9 g.; m. p. 210°) separated in a few seconds,

were collected, and crystallised from 2-ethoxyethanol, giving colourless needles, m. p. 213—214° (Found: C, 67·0; H, 5·6; S, 11·8. Calc. for $C_{11}H_{13}N_3S$: C, 66·9; H, 5·6; S, 11·9%). The thiosemicarbazone from *p*-anisaldehyde obtained in the same way formed colourless fibrous needles, m. p. 178°, from alcohol (Found: C, 63·9; H, 5·6; S, 11·0. Calc. for $C_{12}H_{15}ON_3S$: C, 64·2; H, 5·7; S, 10·7%). Cattelain (*loc. cit.*) gives for these thiosemicarbazones, m. p. 214·5° and 178° respectively.

2-*p*-*Methoxybenzylthiosemicarbazide* (III; R = OMe).—This *compound*, prepared as above, crystallised from alcohol in colourless needles, m. p. 193° (Found: C, 51·1; H, 6·5; N, 20·1; S, 14·8. $C_9H_{13}ON_3S$ requires C, 51·2; H, 6·2; N, 19·9; S, 15·2%).

The following thiosemicarbazides were prepared by the method of Baird *et al.* (*loc. cit.*): 4-benzyl- (IV; R = H), colourless needles, m. p. 128°, from alcohol [benzylidene derivative (prepared as for the 2-isomer) crystallised from alcohol in colourless needles, m. p. 134°], 4-*p*-*methoxybenzyl*- (IV; R = *p*-OMe), colourless needles, m. p. 130°, from alcohol (Found: C, 51·5; H, 6·4; S, 15·1. $C_{10}H_{15}ON_3S$ requires C, 51·2; H, 6·2; S, 15·2%), 4-*isopropyl*-, colourless prisms, m. p. 96°, from benzene (Found: C, 36·1; H, 8·2; S, 24·4. $C_4H_{11}N_3S$ requires C, 36·1; H, 8·3; S, 24·1%) [*p*-*dimethylaminobenzylidene* derivative, sulphur-yellow plates, m. p. 202°, from alcohol (Found: C, 59·3; H, 7·8. $C_{13}H_{20}N_4S$ requires C, 59·1; H, 7·6%)], 4-n-*butyl*-, colourless leaflets, m. p. 70°, from benzene–light petroleum (b. p. 60—80°) (Found: S, 21·7. $C_4H_{13}N_3S$ requires S, 21·8%) [*p*-*dimethylaminobenzylidene* derivative, pale yellow leaflets, m. p. 146°, from alcohol (Found: C, 60·8; H, 8·0. $C_{14}H_{22}N_4S$ requires C, 60·4; H, 7·9%)], 4-*isobutyl*-, colourless leaflets, m. p. 68°, from light petroleum (b. p. 60—80°) (Found: S, 22·2. $C_5H_{13}N_3S$ requires S, 21·8%) [*p*-*dimethylaminobenzylidene* derivative, pale yellow flat needles, m. p. 174°, from alcohol (Found: C, 60·5; H, 7·9. $C_{14}H_{22}N_4S$ requires C, 60·4; H, 7·9%)], and 4-*sec.*-*butyl*-*thiosemicarbazide*, colourless prisms, m. p. 52°, from benzene (Found: S, 22·2. $C_5H_{13}N_3S$ requires S, 21·8%) [*p*-*dimethylaminobenzylidene* derivative, greenish-yellow needles, m. p. 161—162°, from alcohol (Found: C, 60·5; H, 7·8. $C_{14}H_{22}N_4S$ requires C, 60·4; H, 7·9%)].

The following thiosemicarbazides were prepared by the method of Busche, Opfermann, and Walther (*Ber.*, 1904, **37**, 2315): 2-*methyl*-4-*isopropyl*-, fine colourless needles, m. p. 107°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 41·1; H, 9·0. $C_5H_{13}N_3S$ requires C, 40·8; H, 8·8%) [*p*-*dimethylaminobenzylidene* derivative, yellow plates, m. p. 150°, from alcohol (Found: C, 60·1; H, 7·9. $C_{14}H_{22}N_4S$ requires C, 60·4; H, 7·9%)], and 2-*methyl*-4-n-*butyl*-*thiosemicarbazide*, glistening plates, m. p. 50°, from light petroleum (b. p. 60—80°) (Found: C, 45·0; H, 9·1. $C_6H_{15}N_3S$ requires C, 44·7; H, 9·2%) [*p*-*dimethylaminobenzylidene* derivative, almost colourless needles, m. p. 118°, from alcohol (Found: C, 61·6; H, 8·1. $C_{15}H_{24}N_4S$ requires C, 61·6; H, 8·2%)].

Oxidation of 1-*Benzylthiosemicarbazide*.—1-Benzylthiosemicarbazide (1·8 g.) in 10% acetic acid (50 c.c.) was heated at 50° and stirred vigorously, and ferric chloride (anhydrous; 6·4 g.) in water (30 c.c.) added during a few minutes. A solid which separated was collected after cooling (0·9 g.; m. p. 154°), and crystallised from aqueous alcohol, giving colourless needles (0·7 g.) of benzaldehyde thiosemicarbazone, m. p. 162° not depressed by admixture with an authentic specimen (Found: S, 18·0. Calc. for $C_8H_9N_3S$: S, 17·9%). Using twice as much ferric chloride, the thiosemicarbazone (0·2 g.), m. p. 162—163°, was isolated as previously. The original filtrates were made alkaline with ammonia, boiled to coagulate the iron oxides, and filtered. The gelatinous solid was dried in a vacuum, powdered, and extracted with ether in a Soxhlet apparatus. The solvent was evaporated and the residue crystallised from aqueous alcohol, giving colourless glistening prisms (0·4 g.), of 2-amino-5-phenyl-1:3:4-thiadiazole, m. p. 226° not depressed by an authentic sample (Part I, *J.*, 1949, 1163) (Found: C, 54·0; H, 4·1. Calc. for $C_8H_7N_3S$: C, 54·2; H, 3·9%).

In similar experiments, 1-*p*-methoxybenzylthiosemicarbazide (2·2 g.) gave *p*-anisaldehyde thiosemicarbazone (1·0 g.), m. p. 169° (Found: S, 15·5. Calc. for $C_9H_{11}ON_3S$: S, 15·3%), and 1-*p*-ethylsulphonylbenzylthiosemicarbazide (2·7 g.) gave the corresponding thiosemicarbazone (2·0 g.), m. p. 226° (Found: S, 23·5. Calc. for $C_{10}H_{13}O_2N_3S_2$: S, 23·6%).

Oxidation of 2-*Benzylthiosemicarbazide*.—2-Benzylthiosemicarbazide (1·8 g.) was oxidised as described for the 1-isomer. Bleaching of the ferric chloride solution ceased after the addition of 18 c.c. and, after 10 minutes' stirring, the solid was collected and crystallised from alcohol, giving colourless needles (0·5 g.) of the 2-benzyl-1-benzylidenethiosemicarbazide, m. p. 212° not depressed by the compound prepared as above (Found: C, 67·1; H, 5·7; S, 12·0%).

Oxidation of 4-*Benzylthiosemicarbazide*.—4-Benzylthiosemicarbazide (1·8 g.) was oxidised as described for the 1-isomer. An intense purple colour was produced by the first few drops of ferric chloride solution, followed by the separation of a black oil. The oil was extracted with ether and distilled, giving benzyl *iso*thiocyanate (1·0 g.), b. p. 138—140°/20 mm. (Found: S, 21·8. Calc. for C_8H_7NS: S, 21·5%). Identification was confirmed by shaking this oil (0·5 g.) with alcohol (1·0 c.c.) and 50% hydrazine hydrate (2·0 c.c.), whereafter, on removal of the solvent, 4-benzylthiosemicarbazide, colourless needles (0·25 g.), m. p. 130° (from alcohol), was obtained (Found: S, 17·5. Calc. for $C_8H_{11}N_3S$: S, 17·7%).

Similar reactions were carried out with 4-ethylthiosemicarbazide, which gave ethyl *iso*thiocyanate, b. p. 128—129°/760 mm., 4-*iso*propylthiosemicarbazide, which gave *iso*propyl *iso*thiocyanate, b. p. 134—135°/760 mm., 4-*iso*butylthiosemicarbazide, which gave *iso*butyl *iso*thiocyanate, b. p. 164—168°/760 mm., 2-methyl-4-*iso*propylthiosemicarbazide, which gave *iso*propyl *iso*thiocyanate, b. p. 134—135°/760 mm., and 4-phenylthiosemicarbazide, which gave phenyl *iso*thiocyanate, b. p. 106—107°/20 mm. In each case the identity of the *iso*thiocyanate was checked by reaction with hydrazine and observation of the mixed melting point of the crystallised product with the corresponding thiosemicarbazide.

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328. *Strychnine and Brucine. Part LI. Oxypseudostrychnine.*

By C. A. Friedmann.

Both strychnine and *pseudo*strychnine, on catalytic oxidation in presence of ammoniacal solutions of a cobalt salt, afford a carbinol-amine, oxy*pseudo*strychnine, which contains one atom of oxygen more than *pseudo*strychnine.

Evidence is adduced for the conclusion that this base is either *pseudo*strychnine *N*-oxide or a substituted hydroxylamine containing the grouping C(OH)–O–N.

Before discovery of the elegant method of obtaining *pseudo*strychnine from strychnine *N*-oxide (Bailey and Robinson, *J.*, 1948, 703), attempts were made to improve upon the catalytic oxidation process (Leuchs, *Ber.*, 1937, **70**, 1543) by substitution of other catalysts for copper sulphate. During this work it was observed that a solution of strychnine in chloroform, when shaken in the presence of a cobalt salt and ammonia, rapidly absorbed two atoms of oxygen; under similar conditions *pseudo*strychnine absorbed one atom of oxygen, affording the same product.

The new base, $C_{21}H_{22}O_4N_2$, m. p. 246°, could be prepared in twenty-four hours and in yields of up to 70% by the use of oxygen freshly prepared from potassium chlorate and manganese dioxide. Obtained from this source, the oxygen contained chlorine and its oxides, which probably served as carriers, since the rate of absorption decreased rapidly if the oxygen had been stored over water for a few days.

Like *pseudo*strychnine, the new base, termed oxy*pseudo*strychnine, is a carbinol-amine and forms ethers on attempted recrystallisation from simple alcohols. These ethers are formed less readily, and are also less stable, than those from *pseudo*strychnine. Thus, when kept for 3—4 weeks in a desiccator, or when dried at 140°/15 mm. for three hours, they revert to the carbinol-amine, m. p. 246°, probably as a result of hydrolysis by the liberated water of crystallisation usually present.

Unlike *pseudo*strychnine, however, this base has not been obtained in two isomeric forms, nor does it afford either an *O*- or a *N*-acetyl derivative. It is not merely *pseudo*strychnine containing a molecule of water of crystallisation, as that substance, $C_{21}H_{22}O_4N_2,H_2O$, has been isolated from the mother-liquors and readily affords the known *pseudo*strychnine.

Oxy*pseudo*strychnine affords a perchlorate, methoperchlorate, and dihydro-derivative, all of which contain an atom of oxygen more than the corresponding *pseudo*strychnine derivatives. The ease with which the dihydro-derivative is formed indicates that the original strychnine double bond was not involved, *e.g.*, in epoxide formation.

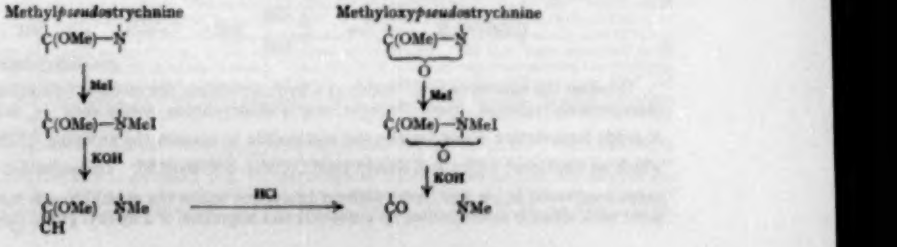
A diagnostic reaction for the character of the second oxygen atom has not been found, the base being inert to reagents for the usual oxygen-containing functional groups.

The most significant difference between the new base and *pseudo*strychnine is the comparative stability of the former to acid reducing agents, whereas *pseudo*strychnine in these circumstances is readily converted into strychnine.

Either zinc dust or tin with hydrochloric acid, and sulphur dioxide in chloroform are without action. Failure to react with the last reagent would suggest that the substance is not a *N*-oxide since strychnine *N*-oxide, in these circumstances, readily reverts to strychnine.

Alkaline reducing agents on the other hand, *e.g.*, metallic sodium in moist chloroform, readily convert it into *pseudo*strychnine.

Like *O*-methyl*pseudo*strychnine, the methyl ether of the new base adds methyl iodide to form *O*-methyloxy*pseudo*strychnine methiodide. Treatment of this methiodide with alcoholic potassium hydroxide or sodium methoxide does not afford the expected methine but gives instead *N*-methyl*chanopseudo*strychnine, m. p. 263°, which in the parallel *pseudo*strychnine degradation can only be obtained by hydrolysis of the des-base under acid conditions:



The action of aqueous ammonia on methyloxy*pseudo*strychnine methiodide does not afford the *chano*-derivative, indicating that the substance is in fact a methiodide and not merely *N*-methyl*chanopseudo*strychnine hydriodide, $\begin{matrix}\text{CO}\\|\\\text{NMe,HI}\end{matrix}$.

The fact that the new base can be obtained from *pseudo*strychnine by catalytic oxidation and that the two methoxy-methiodides can be equated in methyl*chanopseudo*strychnine emphasises the close relationship of the two series.

The most probable structures for the new base in the light of the available evidence are (*a*) that it is *pseudo*strychnine *N*-oxide which, for some reason, has unusual stability to acid reducing agents, or (*b*) that the initially formed *N*-oxide, being an allylamine oxide, is isomerised in the alkaline medium to a substituted hydroxylamine in a manner analogous to that in which methylallylaniline *N*-oxide has been shown to give phenylmethylallylhydroxylamine (Meisenheimer, *Ber.*, 1919, **52**, 1667):

$$\begin{matrix}\text{CH}_2\text{:CH·CH}_2\text{·NPhMe}\\|\\\text{O}\end{matrix} \longrightarrow \text{CH}_2\text{:CH·CH}_2\text{·O·NPhMe}$$

Oxy*pseudo*strychnine would then be obtained according to the scheme

$$\begin{matrix}\text{C(OH)·N·CH}_2\text{·C:CH-}\\|\\\text{O}\end{matrix} \longrightarrow \text{C(OH)·O·N·CH}_2\text{·C:CH-}$$

*pseudo*Strychnine *N*-oxide has hitherto been unknown. Leuchs (*Ber.*, 1944, **77**, 403) has shown that treatment of *pseudo*strychnine with acidic hydrogen peroxide affords a neutral product which is not a *N*-oxide but contains the group ·CO—N< and does not give the Otto reaction.

If oxy*pseudo*strychnine is a *N*-oxide, it is necessary to account for the extreme stability towards acid reducing agents. The most probable explanation would be that chelation occurs in acid but not in alkaline medium, between the N→O and the contiguous hydroxyl group:

$$\text{-C}\begin{matrix}\diagup\text{O—H→O}\\\diagdown\end{matrix}\text{N-}$$

The additional assumption must then be made that the existence of N→O in the molecule does not materially affect ether formation at the *pseudo*strychnine hydroxyl group.

In other respects, too, oxy*pseudo*strychnine does not behave as a normal *N*-oxide. Thus, in distinction from strychnine *N*-oxide, it is almost completely insoluble in one-hundred times its weight of hot neutral 6% hydrogen peroxide. Boiling for an hour with this reagent affords mainly unchanged material, together with traces of a neutral product insoluble in dilute sulphuric acid. This neutral substance affords the Otto reaction; therefore aromatisation of the indole skeleton could not have occurred as in the case of Leuchs's "strychnone."

Acidic hydrogen peroxide, on the other hand, oxidises the base to a substance which has not been obtained pure, but is soluble in both acids and alkalis and may therefore be an amino-acid.

If, however, hydroxylamine formulation is postulated, then the stability of oxy*pseudo*strychnine towards acid reducing agents must be attributed to the closely knit ring system $\text{-}\overset{\lceil R_1 \rceil}{\underset{\lfloor R_2 \rfloor}{\text{C}}}\text{-O-N}$, since normal trisubstituted hydroxylamines do not usually behave in this manner.

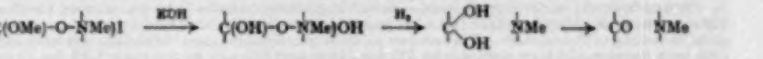
The formation of *pseudo*strychnine from oxy*pseudo*strychnine by reduction with metallic sodium would then probably proceed according to the scheme:

$$\text{C(OH)-O-N} \xrightarrow{H_2} \text{C}\begin{matrix}\text{OH}\\\text{OH}\end{matrix}\text{NH} \xrightarrow{-H_2O} \text{CO NH}$$

*pseudo*Strychnine

Whether the substance is a *N*-oxide or a hydroxylamine, the mode of formation of *N*-methyl*chanopseudo*strychnine from *O*-methyloxy*pseudo*strychnine methiodide is not clear. The *N*-oxide formulation would require the methiodide to contain the grouping $\text{C(OMe)-}\overset{+}{\text{N}}\text{(OMe)}\}\text{I}$, which on treatment with alkali should yield $\text{C(OMe)-N(OMe)}\}\text{OH}$. Isomerisation to a *N*-methyl *chano*-compound is, on this basis, without precedent unless the assumption is made that treatment with alkali is accompanied by reduction and migration of a methyl group from O to N.

The hydroxylamine structure, on the other hand, whilst also requiring the assumption of reduction during treatment with alkali, would proceed without migration of a methyl group:



An obvious difference between the two possible structures is that, on the basis of the hydroxylamine formulation, the *O*-methyl methiodide should contain one *O*- and one *N*-methyl group, whereas the *N*-oxide structure would require two *O*-methyl groups. Zeisel estimation was, however, inconclusive, as at 360° it indicated only 1·3 methyl groups.

A definite formulation for the structure of oxy*pseudo*strychnine cannot be indicated at this stage since neither structure satisfactorily explains all the transformations. Further evidence will be sought.

Experimental.

Oxypseudostrychnine.—Strychnine (50 g.), dissolved in chloroform (200 c.c.), was shaken, in the dark, in presence of freshly prepared oxygen (from potassium chlorate and manganese dioxide) with a catalyst consisting of cobalt chloride (30 g.), ammonia (25 c.c.; *d* 0·88), and water (300 c.c.).

After 8 hours, 1·5 l. of oxygen had been absorbed, and in 30 hours 3·2 l. (two atomic equivalents), the greenish-blue aqueous layer becoming reddish-brown. Thereafter absorption ceased.

The reaction mixture was acidified with 2*N*-hydrochloric acid, the chloroform removed on a steam-bath, and the resulting solution diluted with water (200 c.c.). After 4 hours at 0°, the liquid was filtered from a little neutral material and the filtrate made alkaline with aqueous ammonia. A pale brown base separated (m. p. 235—245°) which was dissolved in 2*N*-hydrochloric acid (200 c.c.) and, after treatment with Norite, was reprecipitated with concentrated aqueous ammonia from the cold solution.

The resulting white precipitate was collected, well washed with water, and redissolved in the minimum of 0·1*N*-hydrochloric acid. To this solution was added sodium acetate (10 g.), followed by a saturated solution of potassium hydrogen carbonate. The precipitated oxypseudo*strychnine*, which separated in a still acid medium, was collected and well washed with water. After being dried at 100°, it was recrystallised from ether–chloroform to give fine, white needles (35 g.), m. p. 245—246° (after drying at 100°) (Found: C, 65·2; H, 6·5. $C_{21}H_{22}O_4N_2,H_2O$ requires C, 65·6; H, 6·25%).

*pseudo*Strychnine (8 g.), m. p. 233°, dissolved in chloroform (50 c.c.), when treated with a catalyst consisting of cobalt chloride (4 g.) and aqueous ammonia (5 c.c.; *d* 0·88) in water (200 c.c.), in presence of freshly prepared oxygen, absorbed 300 c.c. (one atomic equivalent) in 9 hours. The product was worked up as above and afforded oxy*pseudo*strychnine (6 g.), m. p. 246°, which was not depressed on admixture with the material prepared as above.

O-*Methyl*oxypseudo*strychnine.*—A solution of oxy*pseudo*strychnine (1 g.) in methyl alcohol (10 c.c.) was boiled for 5 minutes. Water was added to the hot solution until it became slightly turbid. On cooling, long needles separated, which were collected and dried at 80°/15 mm. (yield, 0·8 g.; m. p. 181—182°). When dried at higher temperatures, *e.g.*, 120°, the methyl ether reverted to the base, m. p. 246°, which, on recrystallisation from 80% methanol, again afforded the *methyl ether*, m. p. 181—182° (Found: C, 66·5; H, 6·55. $C_{22}H_{24}O_4N_2,H_2O$ requires C, 66·3; H, 6·5%).

On recrystallisation from absolute methyl alcohol, a methyl ether not containing water of crystallisation was isolated, having m. p. 174—175° (Found: C, 69·8; H, 6·7. $C_{22}H_{24}O_4N_2$ requires C, 69·5; H, 6·3%), $[\alpha]_D^{20}$ −90° (*c*, 0·0765 in chloroform).

O-*Ethyl*oxypseudo*strychnine.*—Oxy*pseudo*strychnine (1 g.) was refluxed with absolute ethyl alcohol (30 c.c.) for 3 hours. The resulting clear solution was concentrated to small volume (5 c.c.) from which, on cooling, white needles of the *ethyl ether*, m. p. 202—204° (0·75 g.), separated (Found: C, 70·5; H, 6·95; N, 7·5. $C_{23}H_{26}O_4N_2$ requires C, 70·0; H, 6·6; N, 7·1%).

*Methyl*pseudo*strychnine Hydrate.*—The still acid mother-liquors from which oxy*pseudo*strychnine had been precipitated were basified with aqueous ammonia, and the resulting precipitate was collected and extracted with 50% methanol (150 c.c.). The cooled solution was filtered from unchanged strychnine and concentrated to small bulk. On cooling, yellowish crystals of *methyl*pseudo*strychnine hydrate* separated, having m. p. 150—152°, which, after treatment with charcoal in methyl alcohol and 3 further crystallisations from 50% methanol, had m. p. 157—158° (0·4 g.) (Found: C, 68·7; H, 6·45; N, 6·85. $C_{23}H_{26}O_4N_2,H_2O$ requires C, 69·1; H, 6·8; N, 7·3%). These crystals had m. p. 135—138° when mixed with methyloxy*pseudo*strychnine, m. p. 174—175°. On dissolution in dilute hydrochloric acid and reprecipitation with aqueous ammonia, this substance afforded *pseudo*strychnine, m. p. 233°, which could be converted into methyl*pseudo*strychnine, m. p. 198—200°, by recrystallisation from methyl alcohol.

*Methyldihydro-oxy*pseudo*strychnine.*—Oxy*pseudo*strychnine (1 g.), dissolved in dilute acetic acid (30 c.c.), was shaken with platinum oxide (0·1 g.) in an atmosphere of hydrogen. 150 C.c. were absorbed in 30 minutes and a further 25 c.c. in 60 minutes (1 mol.). The resulting solution was filtered from the catalyst, and the base precipitated with aqueous ammonia and dried. The dihydro-compound had m. p. 199° and was converted into the *methyl ether* by recrystallisation from 80% methyl alcohol, forming colourless needles (0·9 g.) of m. p. 142—143° (Found: C, 66·2; H, 6·7. $C_{22}H_{24}O_4N_2,H_2O$ requires C, 66·0; H, 7·0%). The Otto reaction was positive.

*Oxy*pseudo*strychnine Perchlorate.*—Methyloxy*pseudo*strychnine (0·3 g.), m. p. 181°, was dissolved in hot 5% perchloric acid (10 c.c.) and set aside. White needles separated, which were taken up in hot water (10 c.c.) containing one drop of perchloric acid. After being then boiled for two minutes, the solution was filtered and set aside. White prisms separated which were collected and dried at 100°/16 mm. They had m. p. *ca.* 260° (decomp.) (0·28 g.) (Found: C, 54·2; H, 5·3; N, 6·0. $C_{21}H_{22}O_4N_2,HClO_4$ requires C, 53·95; H, 4·9; N, 6·0%).

Preparation of the perchlorate in cold solution and recrystallisation from cold water containing three drops of perchloric acid by evaporation of the solvent at 20°/15 mm. afforded the same perchlorate (Found: C, 53·8; H, 5·2; N, 6·0%).

Oxypseudostrychnine Methoperchlorate.—Methyloxy*pseudo*strychnine (1 g.) was warmed for 15 minutes with a solution of methyl sulphate (1 c.c.) in benzene (10 c.c.). The methosulphate separated as an oily gum, on cooling of the solution. The benzene solution was decanted, and the residue was washed 3 times with pure benzene and then treated with 5% perchloric acid (20 c.c.) on the water-bath for 15 minutes. On cooling, white prisms separated, which were recrystallised from water containing a few drops of perchloric acid; yield, 1·1 g.; m. p. 240° (Found: C, 55·1; H, 5·0. $C_{21}H_{22}O_4N_2,CH_4ClO_4$ requires C, 54·9; H, 5·2%).

Attempted isomerisation of oxy*pseudo*strychnine by repeated boiling in concentrated hydrochloric acid and reprecipitation from the hot solution with aqueous ammonia (*d* 0·88) afforded only unchanged oxy*pseudo*strychnine, m. p. 246°.

Action of Cobalt Chloride Catalyst and Oxygen on N-Methylchanopseudostrychnine.—*N*-Methylchano*pseudo*strychnine (5 g.) in chloroform (50 c.c.) was treated with a catalyst made from cobalt chloride (5 g.) and aqueous ammonia (5 c.c.; *d* 0·88) dissolved in water (150 c.c.). Shaking for one week in presence of freshly prepared oxygen did not result in any absorption of the gas.

Reduction of Oxypseudostrychnine.—(i) *With zinc dust and hydrochloric acid.* Oxy*pseudo*strychnine (1 g.) was dissolved in 2*N*-hydrochloric acid (50 c.c.) and zinc dust (5 g.) added during 30 minutes. The reaction mixture was heated on a steam-bath for 5 hours, at the end of which no further reaction could be observed. The resulting product was diluted with water (150 c.c.), filtered, and made alkaline with aqueous ammonia. The ensuing precipitate was collected, dried, and extracted with chloroform. The extract, after removal of solvent, was twice recrystallised from methanol whereafter it had m. p. 181—182° (0·7 g.) and showed no depression of the m. p. on admixture with methyloxy*pseudo*strychnine.

(ii) *With tin and hydrochloric acid.* Substitution of granulated tin for zinc dust in the above reduction afforded only unchanged oxy*pseudo*strychnine.

(iii) *With sulphur dioxide.* Oxy*pseudo*strychnine (2 g.) was dissolved in moist chloroform (30 c.c.), and sulphur dioxide was bubbled through the solution for 1 hour. The resulting product, after removal of chloroform, was taken up in *N*-hydrochloric acid (25 c.c.) and reprecipitated with aqueous ammonia. The precipitate was collected, dried, and recrystallised from chloroform to which sufficient ether to induce turbidity had been added. White needles separated (1·8 g.), which had m. p. 245—246° and were identical (mixed m. p.) with the starting material.

(iv) *With sodium.* Oxy*pseudo*strychnine (1 g.) was dissolved in moist chloroform (20 c.c.), and freshly cut sodium (0·5 g.), from which most of the kerosene had been removed, was added in the form of a pellet wrapped in a piece of copper gauze. When the gas evolution had ceased, the wire gauze was removed and the chloroform evaporated on the water-bath. Dilute hydrochloric acid (10 c.c.) was added, the solution filtered, and the filtrate basified with aqueous ammonia. The white precipitate was dried and recrystallised from chloroform–ether, to give white needles, m. p. 233°. These were identical (mixed m. p.) with *pseudo*strychnine. Recrystallisation from methyl alcohol afforded colourless needles, m. p. 198—200°, identical with methyl*pseudo*strychnine.

Behaviour towards Hydrogen Peroxide.—A suspension of methyloxy*pseudo*strychnine (1 g.) in neutral 6% hydrogen peroxide (100 c.c.) was boiled under reflux for an hour. The hot solution was filtered from unchanged material (0·97 g.), and the filtrate concentrated under reduced pressure to 15 c.c. After being kept overnight in a refrigerator, the crystals which had separated (0·008 g.) were collected and dried. They had m. p. 222—225°, unchanged by recrystallisation from methanol. This substance was insoluble in dilute acids and was unaffected by sulphur dioxide in chloroform. It probably contained N(*b*)–CO. There was insufficient material for analysis, but it was shown to afford a positive Otto reaction.

A solution of methyloxy*pseudo*strychnine (0·75 g.) in 6% hydrogen peroxide (100 c.c.) and concentrated hydrochloric acid (2 c.c.) was boiled for 20 minutes, the solution becoming dark red. After concentration to 20 c.c., the solution was almost neutralised with aqueous ammonia, a brown amorphous product separating which redissolved in excess of aqueous ammonia.

Treatment of this amorphous product for an hour with charcoal in methyl-alcoholic hydrochloric acid gave, after removal of suspended matter and adjustment of the acidity to pH 6, a pale brown amorphous material which darkened when kept and could not be obtained pure, but could, in view of its solubility in both dilute acids and alkalis, be an amino-acid.

O-*Methyl*oxy*pseudo*strychnine *Methiodide.*—Methyloxy*pseudo*strychnine (1·8 g.), m. p. 181°, after being kept in a desiccator over sulphuric acid for 1 week, was treated for 3 days at room temperature with dry, freshly distilled methyl iodide (15 c.c.). The excess of reagent was removed on the water-bath, and the residue taken up in methanol containing a few drops of *N*/5-sodium thiosulphate. The solution was concentrated to small volume, filtered, and allowed to cool. White prisms separated, which were recrystallised from 80% methanol to give a *methiodide* (2 g.), m. p. 224—226° (after drying on a water-bath) (Found: C, 49·3; H, 5·5; N, 5·5; OMe and NMe, 3·5. $C_{23}H_{27}O_4N_2I,2H_2O$ requires C, 49·5; H, 5·6; N, 5·0; OMe and NMe, 5·4%). The mother-liquor afforded 0·05 g. of the same methiodide, but no compound analogous to *N*-methyl*chano*pseudostrychnine hydriodide could be obtained. A solution of this methiodide, when treated with aqueous ammonia, gave no free base and was therefore not a hydriodide.

Treatment with Alcoholic Potassium Hydroxide.—Methyloxy*pseudo*strychnine methiodide (2 g.) in methanol (25 c.c.) was treated with potassium hydroxide (2 g.) in boiling water (5 c.c.). After 5 minutes a voluminous precipitate (1·3 g.) separated. The crude material, after being dried at 100°, had m. p. 260° and on recrystallisation from methanol m. p. 263°. It was (mixed m. p.) identical with *N*-methyl*chano*-*pseudo*strychnine and was unchanged by prolonged boiling with 10% hydrochloric acid.

Attempted Acetylation of Oxypseudostrychnine.—Dry oxy*pseudo*strychnine (1 g.), m. p. 246°, was refluxed with acetic anhydride (10 c.c.) and pyridine (3 c.c.) for 3 hours. The reaction mixture was poured into water and neutralised with aqueous ammonia. The resulting precipitate was collected, dried, washed with ether, and recrystallised from 80% methanol. The product (0·8 g.) had m. p. 180° and was identical (mixed m. p.) with methyloxy*pseudo*strychnine.

Replacement of the acetic anhydride and pyridine by (i) acetic anhydride alone, (ii) acetic anhydride and anhydrous sodium acetate, (iii) acetic anhydride and one drop of sulphuric acid, (iv) acetyl chloride, or (v) acetyl chloride and acetic anhydride yielded only unchanged material in each case.

Attempted Dehydration of Oxypseudostrychnine.—Oxy*pseudo*strychnine (0·5 g.) was heated at 130°/15 mm. for 3 hours. The product was recrystallised from anhydrous chloroform–ether, to yield unchanged starting material. Oxy*pseudo*strychnine (2 g.) and anhydrous potassium hydrogen sulphate were therefore heated together for 30 minutes at 175°, and the resulting brown mixture was poured into water, made alkaline, and extracted with chloroform. The resulting brown base was dissolved in methanol and treated with charcoal. Removal of the charcoal and concentration of the brown solution afforded an amorphous solid which gave an amorphous perchlorate and an amorphous picrate, unsuitable for analysis.

Attempted dehydration of methyloxy*pseudo*strychnine by heating it at 140°/15 mm. for 30 minutes afforded oxy*pseudo*strychnine, m. p. 246—247°, which, on recrystallisation from 80% methanol, had m. p. 181—182° and was identical with the starting material.

Oxy*pseudo*strychnine did not react with either an alcoholic solution of potassium ferricyanide or an ethereal solution of methylmagnesium iodide. Refluxing with neutralised alcoholic solutions of semicarbazide hydrochloride or hydroxylamine hydrochloride afforded only unchanged material. Clemmensen reduction with amalgamated zinc and 15% hydrochloric acid did not result in any reduced product. The base did not reduce ammoniacal silver nitrate or Fehling's solution.

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329. *Reactions of the Alkyl-sulphate Ion. Part II. Kinetics and Mechanism of the Reaction with Phenoxide Ion and the Polar Effects of Substituents in the Phenol Nucleus.*

By G. H. GREEN and J. KENYON.

The bimolecular nature of the reaction between alkyl-sulphate ion and phenoxide ion has been confirmed. The reaction takes place in the presence of hydroxide ion and, since this latter reacts with alkyl-sulphate ion at a rate comparable to that of phenoxide ion, it was necessary to derive kinetic expressions for the rate constants of two simultaneous second-order reactions. The reaction is entirely analogous to the corresponding reaction of alkyl halides with phenoxide ion except that, as it takes place between two similarly charged ions and not with an ion and a neutral molecule its velocity increases with increasing ionic concentration. The polar effects of nuclear substituents in the phenol are in the expected direction. Values for relative reactivities of phenols towards methylation by dimethyl sulphate by Hodgson and Nixon (*J.*, 1930, 2166) have been shown to be misleading owing to the superposition of two reaction mechanisms.

THE alkylation of phenols with dialkyl sulphates occurs in two stages :

$$R_2SO_4 + PhO^- \longrightarrow RSO_4^- + PhOR \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$RSO_4^- + PhO^- \longrightarrow SO_4^{--} + PhOR \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

No direct evidence as to mechanism exists but indirect evidence that both stages are bimolecular, involving the phenoxide ion, is obtained from the similarity with the corresponding reactions of the alkyl halides and olefin oxides with phenoxide ion, both of which have been studied in considerable detail. By analogy, the velocity should be decreased by increasing accession of electrons on the α-carbon atom of the alkyl sulphate $R{\cdot}CH_2{\cdot}SO_4^-$ (cf. Woolf, *J.*, 1937, 1172). It is known that more stringent conditions are required with diethyl sulphate than with dimethyl sulphate (Cade, *Chem. Met. Eng.*, 1923, **29**, 319). Furthermore, the velocity should be increased by increasing electron accession to the phenolic oxygen atom (cf. Goldsworthy, *J.*, 1926, 1254; Boyd *et al.*, *J.*, 1914, **105**, 2117; 1919, **115**, 1239).

In an attempt to verify the influence of nuclear substituents in phenol on its reactivity, Hodgson and Nixon (*J.*, 1930, 2166) examined the yields of anisoles produced from 19 phenols on reaction with dimethyl sulphate in aqueous medium under standard conditions. They fail, however, to explain numerous anomalous results : (i) the yield of *m*-tolyl ether is higher than that of the *p*-derivative, (ii) the yields of nitrophenyl ethers are the same as or only slightly less than that of anisole, (iii) the yields of chlorophenyl ethers are higher than that of anisole, (iv) the results for the di- and tri-substituted phenols appear unintelligible, (v) steric effects in the *ortho*-position are very small and absent altogether with *o*-cresol. In an attempt to interpret their results, two of their experiments were repeated, *viz.*, the methylation of phenol and of

p-nitrophenol. On theoretical grounds these two phenols should show a considerable difference in reactivity. The experimental details given by Hodgson and Nixon are not very explicit and minor manipulations were used by us which may or may not have been carried out by them. Hodgson and Nixon obtained 65% of anisole and 55·5% of *p*-nitrophenyl methyl ether, whereas we obtained 87 and 61%, respectively. Although the duplication is not too satisfactory the values are in reasonably good relative agreement. During these experiments the following points emerged: (i) some unchanged phenol is carried over with anisole on steam-distillation from alkaline solution—though the quantity was not large enough to affect the yields materially in these cases, the presence of an *ortho*-substituent in the phenol considerably increases its volatility in steam, and if Hodgson and Nixon did not wash their steam-distillate with alkali, it may account, if only partly, for their relatively high yields of *ortho*-substituted anisoles; (ii) the sodium salts of the nitrophenols are relatively insoluble, and certainly less than 0·2 mole per 100 c.c. In the nitrophenol experiment, the greater part of the sodium salt remained undissolved during the initial 30 minutes' stirring in the cold. During the subsequent heating both the sodium salt and the unchanged dimethyl sulphate settled to the bottom of the vessel. This condition was equivalent to that used by Haworth and Lapworth (*J.*, 1923, **123**, 2986) and also by Hodgson and Nixon (*loc. cit.*) in which the phenol is heated with sodium carbonate and dimethyl sulphate in xylene, *i.e.*, in the absence of water. Under these conditions a different mechanism ensues, the reaction, according to Hodgson and Nixon, being facilitated by electron *recession* from the side chain. This in itself is sufficient to account for the high yields obtained with the nitrophenols and di*ortho*-polyhalogenophenols. It is thus obvious that the results give no true picture of the influence of nuclear substituents on the reactions under discussion.

The study of reaction (1) is complicated by such factors as the immiscibility of the alkylating agent with water (unless methanol is used, in which interaction is far too vigorous at normal temperatures for kinetic study), and the presence of the side reaction with hydroxide ion. The former difficulty does not occur with reaction (2), and this process proceeds at a measurable velocity at temperatures of the order of 100°. The side reaction with hydroxide ion occurs at about the same rate as with phenoxide ion and must be allowed for. By employing a large excess (20-fold or more) of alkali over the phenol to ensure complete dissociation of the latter and a similar excess of alkyl sulphate, the amount of alkyl sulphate consumed by the phenoxide ion being very small compared with that consumed by hydroxide ion, it has been possible to evaluate the rate constants for the two simultaneous second-order reactions and so to study their kinetics.

Calculations.

The rate constants for two simultaneous second-order reactions.

Equal $CH_3{\cdot}SO_4Na$ *and* NaOH *Concentrations.*—

(*A*) $CH_3{\cdot}SO_4Na + OH^- \xrightarrow{k'} CH_3{\cdot}OH + NaSO_4^-$.

Let $[CH_3{\cdot}SO_4Na] = [OH^-] = a$

$[CH_3{\cdot}OH] = [NaSO_4^-] = x$ after t seconds.

Then $dx/dt = k'(a - x)^2$

$$k' = x/[ta(a - x)] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (a)$$

k' can be determined experimentally.

(*B*) $CH_3{\cdot}SO_4Na + OPh^- \xrightarrow{k''} CH_3{\cdot}OPh + NaSO_4^-$

If $[OH^-]$ is large compared with $[OPh^-]$, then the $CH_3{\cdot}SO_4Na$ consumed in reaction (*B*) will be negligible compared with that consumed in reaction (*A*), so that the $[CH_3{\cdot}SO_4Na]$ can be considered as $(a - x)$ throughout both reactions.

Let $[OPh^-] = b$

$[CH_3{\cdot}OPh] = y$ after t seconds.

Then $dy/dt = k''(a - x)(b - y)$

Substituting for $(a - x)$ from equation (*a*) and integrating, we have

$$k'' = \frac{k' \log b/(b - y)}{\log (1 + ak't)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (b)$$

Different $CH_3 \cdot SO_4Na$ *and* NaOH *Concentrations.*—

(*A*) $CH_3 \cdot SO_4Na + OH^- \xrightleftarrows{k'} CH_3 \cdot OH + NaSO_4^-$

Let $[CH_3 \cdot SO_4Na] = a$ and $[OH^-] = p$

After t seconds $[CH_3 \cdot SO_4Na] = (a - x)$, and $[OH^-] = (p - x)$

Then $$dx/dt = k'(a - x)(p - x)$$

$$k' = \frac{1}{t(a - p)} \cdot \ln \frac{p(a - x)}{a(p - x)} \quad \ldots \quad (c)$$

k' can be determined experimentally.

(*B*) $CH_3 \cdot SO_4Na + OPh^- \xrightarrow{k''} CH_3 \cdot OPh + NaSO_4^-$

If $[OH^-]$ is large compared with $[OPh^-]$, then the $CH_3 \cdot SO_4Na$ consumed in reaction (*B*) will be negligible compared with that consumed in reaction (*A*), so that $[CH_3 \cdot SO_4Na]$ can be considered as $(a - x)$ in both reactions.

Let $[OPh^-] = b$

$[CH_3 \cdot OPh] = y$ after t seconds.

Then $$dy/dt = k''(a - x)(b - y)$$

Substituting for $(a - x)$ in equation (*c*) and integrating, we have

$$k'' = \frac{2{\cdot}303 \log b/(b - y)}{t(a - p) + \frac{2{\cdot}303}{k'} \log \frac{a - pe^{-kt(a-p)}}{(a - p)}} \quad \ldots \quad (d)$$

In the limiting case when $a = p$, equation (*d*) becomes

$$k'' = \frac{k' \log b/(b - y)}{\log (1 + ak't)}$$

which is identical with equation (*b*).

Experimental.

Determination of Phenols.—Phenols other than those containing an alkyl or alkoxy-group in the *ortho*- or *para*-position were determined with bromate–bromide reagent, anisoles, if present, being first removed by ethereal extraction of the alkaline phenol solution (cf. Ghaswalla and Donnan, *J.*, 1936, 1341). Phenol and *o*- and *p*-alkyl- and -alkoxy-phenols were determined colorimetrically by the method of Folin and Ciocalteu (*J. Biol. Chem.*, 1927, **73**, 627; Snell, "Colorimetric Methods of Analysis," Chapman and Hall, 1936, Vol. 2, p. 348). Anisoles do not interfere.

Phenols Used.—The m. p.s (or b. p.s) and percentage purity (by bromate–bromide titration) were: Phenol, m. p. 41°, purity 100·2%; guaiacol, m. p. 28·5°; *o*-cresol, m. p. 31°; *o*-chlorophenol, b. p. 173°, purity 100·2%; *o*-nitrophenol, m. p. 45—46°, purity 99·0%; *m*-methoxyphenol, b. p. 238°, purity 97·8%; *m*-ethoxyphenol, b. p. 138°/17 mm., purity 96·4%; *m*-cresol, b. p. 96—98°/20 mm., purity 98·9%; *m*-fluorophenol, b. p. 81°/16 mm., purity 91·0%; *m*-chlorophenol, m. p. 30—31°, purity 98·7%; *m*-nitrophenol, m. p. 95·5—96°, purity 99·4%; *p*-methoxyphenol, m. p. 52·5—53°; *p*-ethoxyphenol, m. p. 63·5—64°; *p*-cresol, m. p. 35°; *p-tert.*-amylphenol, m. p. 92—93°; *p*-fluorophenol, m. p. 45°, purity 100·5%; *p*-chlorophenol, m. p. 41·5—43°, purity 100·2%; *p*-bromophenol, m. p. 63·5°, purity 98·8%; *p*-iodophenol, m. p. 92°, purity 100·1%; *p*-nitrophenol, m. p. 112°, purity 100·4%; 3 : 5-dimethoxyphenol (phloroglucinol dimethyl ether), m. p. 35·5—36°, purity 99·5%.

Stability of Phenols in Aqueous Alkali at 100°.—No decomposition or oxidation of any of the phenols used was detected on heating them for one hour in 1·0*N*-sodium hydroxide at 100°.

Metal Alkyl Sulphates.—The preparation of the various metal alkyl sulphates and their quantitative determination have been described in Part I (*J.*, 1950, 1389). The same preparations were used.

Determination of the Rate of Reaction of Alkyl-sulphate Ion with Phenoxide Ion.—The determination of the constant k' for the second-order reaction between alkyl-sulphate ion and hydroxide ion has already been described in Part I.

In general the initial mixture was *N*. with respect to metal alkyl sulphate and alkali, and approx. 0·03*N*. with respect to phenol. The sodium hydroxide and potassium hydroxide were carbonate-free and all solutions were made up with carbon dioxide-free water. The anhydrous metal alkyl sulphate was weighed rapidly into a beaker and transferred with water to a graduated flask, followed by the required quantities of standard 4*N*-alkali and phenol. Aliquots (10 ml.) were pipetted into the reaction-tubes. Alternatively, 5 ml. each of two separate solutions of 2·00*N*-metal alkyl sulphate and approx. 0·1*N*-phenol in 2·00*N*-alkali were used. The reaction was carried out at 100° under conditions identical

with those used in the determination of k' (*q.v.*). The reaction was arrested by plunging the tubes into cold running water. Two or three tubes were taken at zero time for the determination of the initial hydroxide ion concentration by titration with 0·5*N*-hydrochloric acid to phenolphthalein. The phenol did not interfere, except with the nitrophenols, for which it was necessary to carry out a parallel reaction with the nitrophenol absent. Tubes were also withdrawn at zero time and at intervals for determination of the residual phenol.

Owing to the relatively rapid reduction of the methyl-sulphate ion concentration owing to the side reaction with hydroxide ion, the reaction could not usefully be prolonged beyond 4 hours, by which time it had become very slow indeed. This meant that even in the most favourable cases (*e.g.*, the *p*-alkoxyphenols) only 60% of the phenol had reacted, with phenol itself 50%, down to the exceedingly unreactive *o*- and *p*-nitrophenols reacting to the extent of only 2 and 4% respectively. In these last two cases the rate constant is based on the amount which had reacted at one time interval only, *viz.*, 240 minutes. In all other cases the mean value at 4 or more time intervals has been taken. The reaction between ethyl-sulphate ion and phenoxide ion was carried out over 6 hours, in which time some 25% of the phenol had reacted. The detailed results of two typical experiments using equations (*b*) and (*d*) are given in Tables I and II respectively. The complete results are summarised in Tables III and IV.

TABLE I.

Rate of reaction of sodium methyl sulphate with phenol in aqueous alkaline solution at 100° *(equivalent methyl-sulphate and hydroxide ion concentrations).*

Initial concns. of reactants: [NaOH] and [$CH_3{\cdot}SO_4Na$] = 1·000, [phenol] = 0·05.
Phenol determined by Folin and Ciocalteu's method.
0·05*N*-HCl = residual NaOH at zero time = 18·6 ml.: a = 0·923.

Time (mins.).	Residual phenol (mg.).	$\frac{b}{b-y}$	$60ak't$.	$10^3 k'' = \frac{k' \log b/(b-y)}{\log(1+60ak't)}$	Time (mins.).	Residual phenol (mg.).	$\frac{b}{b-y}$	$60ak't$.	$10^3 k'' = \frac{k' \log b/(b-y)}{\log(1+60ak't)}$
0	45·76	—	—	—	145	29·92	1·529	0·9152	7·4
20	41·88	1·093	0·1262	(6·7)	175	28·58	1·601	1·104	7·2
40	39·38	1·162	0·2524	7·5	205	26·90	1·702	1·294	7·4
61	36·76	1·254	0·3850	7·6	240	24·80	1·845	1·515	7·5
85	34·84	1·313	0·5364	7·2					
115	32·16	1·423	0·7257	7·3				Mean	7·4

Notes: (1) k' = 11·35 × 10^{-4} (see Part I).
(2) Owing to expansion of the reaction solution on heating the true volume of the solution is 10·17 ml. (see Part I).

TABLE II.

Rate of reaction of sodium methyl sulphate with phenol in aqueous alkaline solution at 100° *(non-equivalent methyl-sulphate and hydroxide ion concentrations).*

Initial reaction mixture: 5 ml. of solution *A* + 5 ml. of solution *B* (solution *A*: 1·044*N*-NaOH, 0·80*N*-Na_2SO_4, 0·10*N*-phenol; solution *B*: 2·000*N*-$CH_3{\cdot}SO_4Na$).
Phenol determined by bromate–bromide method.

Suppose that the temperature of the reaction mixture be raised to 100° without any reaction taking place. Then when allowance is made for expansion, the concentrations of the reactants become

$$[NaOH] = 0{\cdot}522 \times 10{\cdot}00/10{\cdot}17 = 0{\cdot}513 = p'$$
$$[CH_3{\cdot}SO_4Na] = 1{\cdot}000 \times 10{\cdot}00/10{\cdot}17 = 0{\cdot}983 = a'.$$

0·5*N*-HCl = residual NaOH at zero time = 9·85 ml.: p = 0·484.
Hence drop in [NaOH] = drop in [$CH_3{\cdot}SO_4Na$] from commencement of the reaction to zero time = $(p' - p)$ = 0·513 − 0·484 = 0·029 = c.
Hence [$CH_3{\cdot}SO_4Na$] at zero time = $(a' - c)$ = 0·983 − 0·029 = 0·954 = a.

Time (mins.).	Ml. of 0·1*N*-Br = residual phenol ($b - y$).	$\frac{b}{b-y}$	$2{\cdot}303 \log b/(b-y)$ (*A*).	$60t(a-p)$ (*B*).	(*C*).*	$10^3 k'' = \frac{A}{B+C}$
0	28·35	—	—	—	—	—
20	26·3	1·077	0·07308	564·0	568·0	6·6
50	23·5	1·206	0·1877	1410	1481	6·1
90	20·4	1·390	0·3294	2538	2576	6·4
140	17·8	1·593	0·4657	3949	3846	6·0
200	16·5	1·718	0·5416	5640	5458	(4·9)
					Mean	6·3

* $C = \frac{2{\cdot}303}{k'} \log \frac{a - p_{60t=\text{mean value}} - y}{a - p}$.
$k' = 11{\cdot}35 \times 10^{-4}$.

TABLE III.

Second-order rate constants for the reaction between metal alkyl sulphates and phenoxide ion in aqueous solution at 100°.

Initial phenol concn. approx. 0·03*M*. in all cases except in Expt. 1D where it was 0·025*M*.

Expt.	Metal alkyl sulphate.	Initial concn.	Alkali.	Initial concn.	k'' × 10³.
1A	$CH_3{\cdot}SO_4Na$	1·00	NaOH	1·00	7·4
1B	"	"	"	"	7·4
1C	"	"	"	0·50	6·6 — 4·9 *
1D	"	"	"	"	7·4 — 5·6 *
2	$CH_3{\cdot}SO_4K$	"	KOH	1·00	6·8
3	$C_2H_5{\cdot}SO_4Na$	"	NaOH	"	1·37

* The total ionic concentration (Σ[ion] × charge) was adjusted to 4·00 by the addition of 0·25*M*-Na_2SO_4.

TABLE IV.

Second-order rate constants for the reaction between sodium methyl sulphate and phenoxide ions in aqueous solution at 100°.

Initial concns.: [NaOH] = 1·00, [$CH_3{\cdot}SO_4Na$] = 1·00, [phenol] = approx. 0·03*M*.

Phenol.	k'' × 10³.	Phenol.	k'' × 10³.
Phenol	7·4, 7·4	*p*-Methoxyphenol	10·1
Guaiacol	6·7	*p*-Ethoxyphenol	10·95
o-Cresol	6·7	*p*-Cresol	9·3
o-Chlorophenol	3·0	*p*-*tert*.-Amylphenol	10·5
o-Nitrophenol	0·25	*p*-Fluorophenol	7·2
m-Methoxyphenol	6·0	*p*-Chlorophenol	5·45
m-Ethoxyphenol	6·0	*p*-Bromophenol	5·3, 5·3
m-Cresol	5·3	*p*-Iodophenol	5·1
m-Fluorophenol	4·3	*p*-Nitrophenol	0·5
m-Chlorophenol	4·2	3 : 5-Dimethoxyphenol	5·2
m-Nitrophenol	2·6		

Accuracy of the Results.—Where duplicate runs were carried out the results were in excellent agreement. A number of other experiments (not reported here), in which the mean value of k'' is based on only three values, also confirmed the reproducibility of the results. In general the error of the mean is certainly not greater than 5% for the less reactive phenols and considerably less for the more reactive ones.

Influence of Electrolyte on the Reaction.—Various amounts of anhydrous sodium sulphate were added to 10-ml. portions of a solution containing 1·00*N*-sodium hydroxide, 1·00*N*-sodium methyl sulphate, and 0·10*N*-phenol. After 60 minutes' heating at 100° the residual phenol was determined and approximate values for the rate constant were calculated. The values obtained rose steadily from 8·22 × 10^{-4} with no added sodium sulphate to 8·63 × 10^{-4} in the presence of 2·0*N*-sodium sulphate.

Repetition of Some Experiments of Hodgson and Nixon.—Methyl sulphate (12 ml.) was added to a stirred solution of the phenol (0·1 mole) in sodium hydroxide (50 ml.; 10%), and the stirring continued for 30 minutes. The mixture was transferred to a 250-ml. flask, slowly warmed to 100° in a water-bath (20 minutes), and kept there for 30 minutes. The mixture was distilled in a current of steam until no more anisole came over, then for a further 10 minutes. The anisole was taken up in ether, the ethereal extract washed once with 4% sodium hydroxide solution, the ether evaporated on the steam-bath, and the anisole placed in a steam-oven for 1 hour. After this time no smell of ether was detectable. Yields: anisole, 9·4 g. (87%); *p*-nitroanisole, 9·3 g. (61%).

DISCUSSION.

The absence in all cases of any upward or downward trend in the rate constants calculated from equation (*b*) for two simultaneous second-order reactions confirms the bimolecular nature of the reaction between alkyl-sulphate ion and phenoxide ion. When equation (*d*) was used, however, the value of k'' tended to fall as the reaction proceeded. Since k'' as calculated from this equation is extremely sensitive to small errors in the values of the alkyl-sulphate and hydroxide ion concentrations, it is possible that a refinement in experimental technique may overcome this anomaly. It is extremely unlikely that the divergence is serious enough to throw doubt upon the postulated bimolecular nature of the mechanism.

The reaction, being between two ions of like charge, is accelerated by increasing ionic concentration (see also Part I). No attempt has been made to investigate the matter thoroughly. The accelerating effect of sodium ions appears to be slightly greater than that of potassium ions.

The fall in reaction velocity on passing from methyl to ethyl is due to increasing accession of electrons to the α-carbon atom. The ratio of the rates is approximately 5 : 1, in reasonable

agreement with ratio of 4 : 1 obtained by Woolf (*loc. cit.*) for the relative rates of reaction of methyl and ethyl iodides with sodium eugenoxide in ethyl alcohol at 50°. Comparison of the rates of reaction of the two alkyl sulphates with hydroxide and with phenoxide ions (see Table V) reveals the interesting fact that, contrary to expectation, sodium ethyl sulphate reacts more readily with the latter. A partial distribution of the negative charge over the benzene ring would render phenoxide less reactive than hydroxide ion. The reason for this anomaly is not known.

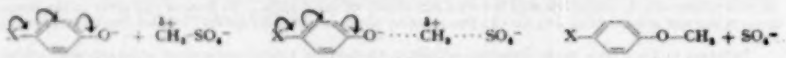
TABLE V.

Second-order rate constants for the reaction of sodium alkyl sulphates with hydroxide and phenoxide ions in aqueous solution at 100°.

Alkyl sulphate.	10^4k for reaction with OH^-.*	OPh^-.
Sodium methyl	11·35	7·4
Sodium ethyl	1·05	1·37

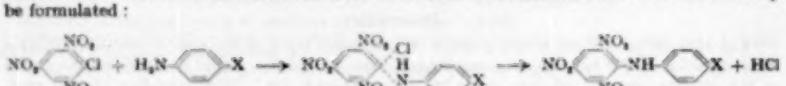
* From Part I.

Influence of Nuclear Substituents.—The influence of nuclear substituents in the phenol is in the expected direction, except for those in the *ortho*-position where considerable steric effects are apparent. This is in contrast to the results of Boyd *et al.* (*loc. cit.*) who did not find appreciable steric hindrance in their reaction of phenoxide ions with ethylene and propylene oxides (except the nitro-group); also the dissociation constants of the *ortho*-substituted phenols are normal (Dippy, Evans, Gordon, Lewis, and Watson, *J.*, 1937, 1421). In the *meta*- and *para*-positions the influence of the substituent is determined solely by the relative magnitude of the inductive and tautomeric effects. It is observed (Table IV) that the reaction rates of the *p*-halogeno-substituted phenols diminish in the order $H > F > Cl > Br > I$; the tautomeric electron-release effects ($+T$) of the halogens diminish in the same order, whereas their inductive effects ($-I$) become more negative in the reverse order. To explain this co-ordination of tautomeric effect with reaction rate it is necessary to consider the electron movements during the course of the reaction. The initial, transitional, and final states of the reactants are as follows:



Initial Transitional Final

The formation of the transitional state is facilitated by the localisation of the negative charge on the phenolic oxygen atom; the formation of the final state requires the localisation of both negative charges on the SO_4 group. *Both* these conditions will be facilitated by electron release from the group X. In only a few other cases has complete inversion of the relative reactivities of the *para*-halogens been observed in reactions facilitated by electron accession to the side chain, and all but one are unimolecular and have one rate-determining stage only. The only bimolecular reaction reported to show complete inversion is that between chloronitrobenzenes and substituted anilines in dilute alcohol (Linke, *Ber.*, 1923, **56**, 848). Although *p*-fluoroaniline was not included there is no reason to doubt that it will fall into line. The reaction may be formulated:



Here again, *both* stages are facilitated by electron release from the group X: (*a*) the attack of the amino-nitrogen atom on the positive nuclear carbon atom, and (*b*) the release of the negatively charged chlorine ion. It may be expected that the reaction of phenoxide ion with dialkyl sulphates, alkyl halides, ethylene oxides, etc., will also exhibit the inverted order of reactivity for the *p*-halogeno-compounds. The inverted order is also to be found in the dissociation constants of phenols, benzoic acids, phenylacetic acids, and phenylboric acids (Dippy, *Chem. Reviews*, 1939, **25**, 151). In these cases the predominant influence is the mesomeric ($+M$) portion of the tautomeric effect reflected in the resonance of the molecule due to a contribution of the quinonoid form, *e.g.*, .

In the case of the phenoxide ion, the oxygen atom already possesses six free electrons and resonance of this type cannot be expected. It must, therefore, be the electromeric ($+E$) effect acting in the initial and transitional states which assists the reaction between phenoxide ion and alkyl sulphate. Summing up we have:

Forces affecting equilibrium constant $-I + M$
Forces affecting reaction constant $-I + E$

If log k for the reaction is plotted against log K for the equilibrium (see Table VI and figure) the points for the substituted phenols lie on a straight line, whereas phenol itself lies considerably off the line. It has been pointed out by Dippy and Watson (*J.*, 1936, 436) that the operation of electromeric effects can cause a divergence from the linear relation between log k and log K.

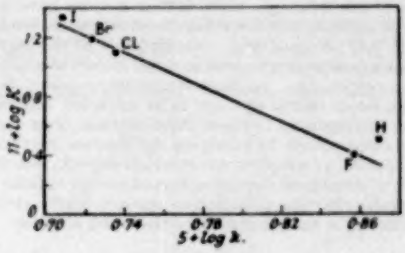
TABLE VI.

Relation between log K *and log* k *for p-halogenophenols.*

Substituent.	$10^{10}K$.*	11 + log K.	$10^{5}k$.	5 + log k.
—	0·32	0·5051	7·4	0·8692
p-F	0·26	0·4150	7·2	0·8573
p-Cl	1·32	1·1206	8·45	0·7364
p-Br	1·55	1·1903	8·3	0·7243
p-I	2·19	1·3404	8·1	0·7076

* K is the dissociation constant in 30% ethanol at 25° (Bennett, Brooks, and Glasstone, *J.*, 1935, 1821). Since the relative dissociation constants of acids are generally independent of both medium and temperature, it is permissible to compare reaction velocities in one medium with dissociation constants in another medium and at a different temperature (Dippy, *Chem. Reviews*, 1939, **25**, 151).

The present reaction provides an addition to the list of benzene side-chain reactions which obey the simple law log K = log K° + $\rho\sigma$ where ρ = reaction constant, σ = substitution constant, and K and K° = rate constants for substituted and unsubstituted reactants respectively (Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, 1940, p. 184;



J. Amer. Chem. Soc., 1937, **59**, 96). By using Hammett's value of σ, values of ρ have been calculated and are given in Table VII. The large divergence of the *p*-fluoro- and *p*-nitrophenols may be due to experimental error—the former owing to the very small difference in rate with unsubstituted phenol, and the latter to the difficulty of measuring its very slow reaction rate with accuracy.

TABLE VII.

Calculated values of ρ *for the reaction between substituted phenoxide ions and sodium methyl sulphate.*

Substituent.	σ.	ρ.	Substituent.	σ.	ρ.
p-OMe	−0·268	0·520	*p*-Cl	0·227	0·585
p-OEt	−0·25	0·682	*p*-Br	0·232	0·624
p-Me	−0·170	0·584	*p*-I	0·276	0·586
m-Me	−0·069	0·723	*m*-F	0·337	0·700
p-F	0·62	(0·180)	*m*-Cl	0·373	0·658
m-OMe	0·115	0·791	*m*-NO_2	0·710	0·640
m-OEt	0·15	0·606	*p*-NO_2	1·27	(0·921)

Mean ρ 0·642.

General Considerations.—Since sodium methyl sulphate reacts with phenoxide and hydroxide ions at roughly the same rate it is obviously of advantage in using this reagent as a methylating agent to maintain the hydroxide ion concentration at as low a level as possible consistent with keeping the phenol dissociated. Highest yields based on the methylating agent and most rapid reaction will be obtained when the alkali is added slowly to a boiling strong solution of phenol and sodium methyl sulphate so that the solution is maintained *just* alkaline all the time. Sodium salts are preferred to the corresponding potassium salts on account of their more rapid reaction and greater solubility.

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BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, February 8th*, 1950.]

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330. *The Reaction of Methyl Radicals with Olefins. Part IV. The Reaction with Tetrafluoroethylene and Vinyl Fluoride.*

By F. A. RAAL and C. J. DANBY.

The rate of polymerisation of tetrafluoroethylene induced by acetaldehyde photolysis is very much greater than that of ethylene under the same conditions. An insoluble solid polymer is produced for which the kinetic results suggest a molecular weight corresponding to about 20 fluoroethylene units. In contrast to the behaviour with the lower olefins the rate of aldehyde photolysis is greatly increased by the presence of fluoroethylene. By analogy with the previous results a chain polymerisation is assumed to be initiated by methyl radicals from the aldehyde photolysis, a fluorinated radical which can initiate further polymerisation being eventually produced by chain transfer. The experimental results require that this radical should be able to induce the decomposition of a molecule of acetaldehyde into carbon monoxide and methane without itself suffering any change in the process.

Vinyl fluoride is also polymerised by aldehyde photolysis, the rate of which is unchanged. This can be explained if every polymerisation chain suffers chain transfer.

IN the previous papers of this series (*J.*, 1949, 2219 *et seq.*) we have considered the reactions which occur when methyl radicals from the aldehyde photolysis interact with the lower olefins. As valuable information was obtained from measurements of the degree of inhibition of the photolysis by the olefin it was necessary to work at temperatures at which the chain length of the aldehyde photolysis was appreciable. At these temperatures (about 300° C.) the formation of high polymers from the lower olefins was not to be expected and the maximum degree of polymerisation observed corresponded to about three ethylene units per molecule. Polytetrafluoroethylene produced commercially by catalysed liquid-phase reaction is very stable to heat, being unchanged and still solid at temperatures at which polyethylene decomposes rapidly. It was therefore of interest to investigate the interaction of methyl radicals with fluoro-substituted olefins as it seemed probable that the propagation reaction might proceed further before the intervention of chain transfer or chain termination than with ethylene.

EXPERIMENTAL.

Methods.—The experimental methods were the same as those described in Part I. The rates of aldehyde photolysis and of olefin polymerisation were obtained separately by a combination of pressure measurements with chemical analysis for unchanged aldehyde. Tetrafluoroethylene and vinyl fluoride were obtained from Imperial Chemical Industries Limited, General Chemicals Division, in glass vessels at atmospheric pressure. They were displaced from the vessels with water, dried with phosphoric oxide, and fractionated between cooled traps, only the middle fractions being collected. Larger quantities of the tetrafluoroethylene polymer were produced in a simple flow apparatus. The gas was passed slowly through a bubbler containing acetaldehyde at −20° and the emerging stream containing about 50 mm. of acetaldehyde vapour allowed to flow through a quartz tube irradiated by a mercury lamp. The polymer formed as a white cloud in the gas, the greater part settling to the bottom of the tube and the remainder adhering to the cooler parts of the wall. About 4 g. of the polymer were obtained in this way.

Results.—(i) *Vinyl fluoride.* The rate of photolysis of 50 mm. of acetaldehyde at 300° in the presence of vinyl fluoride and the rate of the induced polymerisation of the latter are shown in Figs. 1 and 2 as a function of vinyl fluoride pressure. The rate of polymerisation is very similar to that of ethylene under the same conditions. In contrast to the behaviour with ethylene, the rate of aldehyde photolysis is unchanged by the presence of vinyl fluoride, though the latter is polymerised.

(ii) *Tetrafluoroethylene.* Figs. 1 and 2 also give the experimental results for the aldehyde-induced polymerisation of tetrafluoroethylene. Here the rate of polymerisation is almost ten times that of ethylene, and the rate of aldehyde photolysis is greatly accelerated instead of suffering inhibition.

(Owing to the rapid rates of pressure change the initial rates were obtained by plotting pressure–time curves for the early parts of the reaction and drawing tangents at the origin.) Figs. 3 and 4 give the corresponding results obtained with a constant pressure of tetrafluoroethylene (50 mm.) and variable

FIG. 1.

Rate of photolysis of 50 mm. of acetaldehyde in the presence of ethylene, vinyl fluoride, and tetrafluoroethylene. Smooth curve for tetrafluoroethylene is that calculated *from equation* (I).

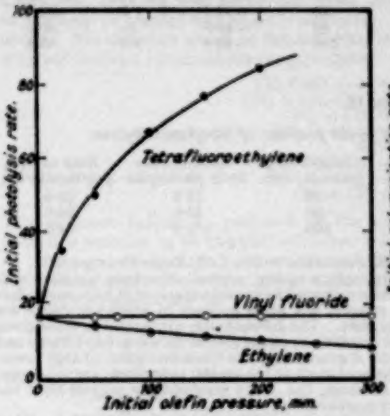


FIG. 2.

Rates of polymerisation of ethylene, vinyl fluoride, and tetrafluoroethylene induced by photolysis of 50 mm. of acetaldehyde. Smooth curve for tetrafluoroethylene is that calculated *from equation* (II).

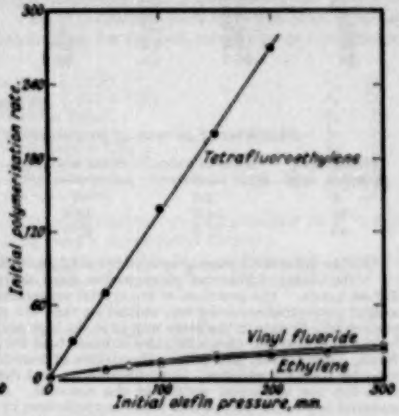


FIG. 3.

Rate of photolysis of acetaldehyde in the presence of 50 mm. of tetrafluoroethylene as function of aldehyde pressure. Smooth curve is that calculated *from equation* (I).

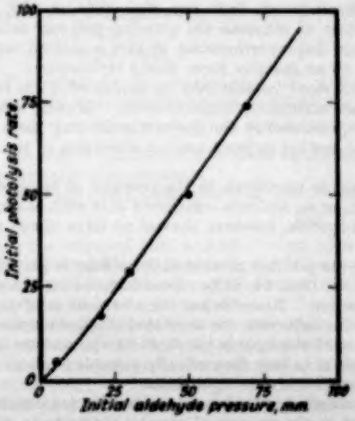
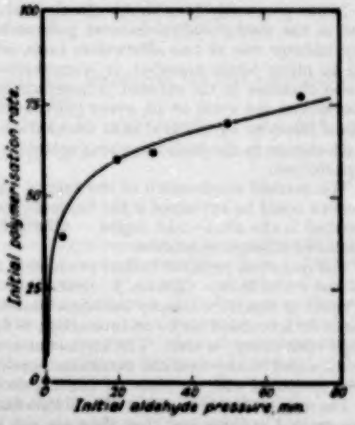


FIG. 4.

Rate of polymerisation of 50 mm. of tetrafluoroethylene induced by acetaldehyde photolysis as function of aldehyde pressure. Smooth curve is that calculated *from equation* (II).



aldehyde pressures. The polymerisation of tetrafluoroethylene is also induced by the photolysis of acetone. The results given in Table I show that the rate of photolysis is not altered by the presence of the olefin.

The photolysis of propaldehyde induces the polymerisation, there being very marked acceleration of the rate of photolysis, as shown by the results in Table II.

TABLE I.

Photolysis of 50 mm. of acetone in presence of tetrafluoroethylene.

(Rates are initial rates and are expressed in terms of the number of mm. of gas reacting in 8 minutes.)

Initial C_2F_4 pressure, mm.	Overall pressure change, mm.	Rate of photolysis.	Rate of C_2F_4 polymerisation.	Initial C_2F_4 pressure, mm.	Overall pressure change, mm.	Rate of photolysis.	Rate of C_2F_4 polymerisation.
0	+ 0·5	1·0	—	80	−30·5	1·0	31·0
10	− 4·0	—	5·4	90	−40·0	—	40·5
30	−15·4	1·2	15·9	100	−46·1	1·2	46·6
50	−25·7	—	26·2				

TABLE II.

Photolysis of 50 mm. of propaldehyde in the presence of tetrafluoroethylene.

Initial C_2F_4 pressure, mm.	Rate of aldehyde photolysis.	Rate of C_2F_4 polymerisation.	Initial C_2F_4 pressure, mm.	Rate of aldehyde photolysis.	Rate of C_2F_4 polymerisation.
0	5·0	—	60	25·5	35·0
20	14·0	12·5	80	28·0	45·0
40	21·5	25·0	100	30·5	54·5

X-Ray diffraction photographs of the solid material were taken by Mr. C. W. Bunn who reports: "The *X*-ray diffraction photographs show sharp, rather spotty, crystal reflections together with diffuse bands. The positions of the crystal reflections correspond to the side-spacings of high-molecular-weight polytetrafluoroethylene, indicating that the material is a linear polymer in which the chains are packed side-by-side in the same way as in the high polymer. The diffuse bands correspond to those given by the high polymer above 20°, and indicate that the crystals are disordered in the same way (Rigby and Bunn, *Nature*, 1949, **164**, 583). The degree of disorder is greater, and the transition point (if any) lower, than for the high polymer; these differences, and the spottiness of the crystal reflections, are consistent with the low molecular weight of the material. In short, the *X*-ray photographs suggest that the material is a linear polymer of tetrafluoroethylene of comparatively low molecular weight."

The solid reaction product had a diffuse melting point of about 220°, which is about 100° below that of the high polymer. The infra-red spectrum showed bands in the regions to be expected for CH and CH_2 vibrations which are absent from the high polymer, otherwise the spectra were rather similar.

DISCUSSION.

It has previously been shown (Danby and Hinshelwood, *Proc. Roy. Soc.*, 1941, *A*, **179**, 169) that in the methyl-radical-induced polymerisation of ethylene the growing polymer radicals may undergo one of two alternative fates, either disproportionation to give a methyl radical and an olefin (chain transfer), or isomerisation to an inactive form (chain termination). The results obtained in the induced polymerisation of vinyl fluoride may be explained if the latter process does not occur at all, every polymer chain undergoing chain transfer. If every methyl radical removed by reaction with the olefin is regenerated in the chain-transfer step there will be no change in the stationary concentration of methyl radicals and no alteration in the rate of photolysis.

The marked acceleration of the rate of aldehyde photolysis in the presence of tetrafluoroethylene could be explained if the fluoroethylene, or an addition compound of it with aldehyde, absorbed in the ultra-violet region. Absorption spectra, however, showed no trace of any such additional absorptive process.

The quantum yield for radical production in the primary process of the aldehyde photolysis is about 0·2 at 3150 A. (Blacet, *J. Amer. Chem. Soc.*, 1942, **64**, 893). Four-fifths of the absorbed radiation is therefore lost by collisional deactivation. Nevertheless the observed acceleration cannot be accounted for by an interaction of fluoro-olefin with the activated aldehyde molecules before their energy is lost. The lifetime of activated aldehyde is too short for this process to be effective and in any case the maximum acceleration in rate theoretically possible is about five times compared with the observed limiting acceleration of over eight times.

The only alternative explanation is that fluoromethyl radicals are considerably more reactive than methyl radicals and that they are not lost in the process of causing aldehyde to react. From what we know of the reaction with ethylene, the induced polymerisation of the fluoroethylene must consist of the successive addition of olefin molecules to the initiating radical so as to build up a large radical. This radical in undergoing chain transfer may either regenerate the initial methyl radical or, alternatively, a radical such as CF_3 from the other end of the molecule.

If the latter, then this fluoromethyl radical might react with aldehyde by one of two alternative processes:

$$CF_3 + CH_3{\cdot}CHO = CF_3 + CH_4 + CO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (a)$$
$$CF_3 + CH_3{\cdot}CHO = CH_3 + CF_3H + CO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (b)$$

The experimental results require no loss of fluoromethyl radicals and preference is therefore given to (*a*). This reaction may be an induced predissociation of the kind suggested by Taylor and Burton (*J. Chem. Physics*, 1939, **7**, 414). It may also be significant that Morris (*J. Amer. Chem. Soc.*, 1944, **66**, 584) found that mixed deuteromethanes were not formed in the pyrolysis of mixtures of normal and deutero-aldehyde. This is consistent with reactions similar to (*a*) above. We therefore arrive at the following mechanism for the polymerisation of tetrafluoroethylene induced by acetaldehyde photolysis:

$$CH_3{\cdot}CHO + h\nu = CH_3 + CHO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad k_1 \quad (1)$$
$$CH_3 + CH_3{\cdot}CHO = CH_4 + CO + CH_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad k_2 \quad (2)$$
$$CH_3 + CH_3 = \text{chain ended} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad k_3 \quad (3)$$
$$CH_3 + nC_2F_4 = R_n \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad k_4 \quad (4)$$
$$R_n = \text{product} + CF_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad k_5 \quad (5)$$
$$CF_3 + CH_3{\cdot}CHO = CF_3 + CO + CH_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad k_2' \quad (2')$$
$$CF_3 + nC_2F_4 = R_n \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad k_4' \quad (4')$$
$$CF_3 + CF_3 = \text{chain ended} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad k_3' \quad (3')$$

(The polymer radical R_n produced by the addition of fluoroethylene molecules to a *methyl* radical is assumed to be identical with that arising from a *fluoromethyl* radical.)

The usual stationary-state treatment of these equations leads to the following expressions for the rate of photolysis (ρ) of aldehyde in the presence of fluoroethylene and for the rate of the induced polymerisation (σ):

$$\rho = C'[A]\left[\left\{[F]^2 + \frac{\rho_0^2}{(C')^2[A]^2}\right\}^{\frac{1}{2}} - [F]\right] + C''[A][F]^{\frac{1}{2}}\left[[F]^2 + \frac{\rho_0^2}{(C')^2[A]^2} - [F]\right]^{\frac{1}{2}} \quad . \quad . \quad (I)$$

where $[A]$ = aldehyde pressure,
$[F]$ = tetrafluoroethylene pressure,
ρ_0 = aldehyde photolysis rate in absence of olefin,
$C' = k_2k_4/2k_3$,
and $C'' = k_2'k_4/(2k_3k_3')^{\frac{1}{2}}$

$$\sigma = \tfrac{1}{2}nK'[F]\left[\left\{[F]^2 + \frac{\rho_0^2}{(C')^2[A]^2}\right\}^{\frac{1}{2}} - [F]\right] + nK''[F]^{\frac{1}{2}}\left[\left\{[F]^2 + \frac{\rho_0^2}{(C')^2[A]^2}\right\}^{\frac{1}{2}} - [F]\right]^{\frac{1}{2}} \quad . \quad (II)$$

where n = average number of olefin molecules incorporated in product,
$K' = (k_4)^2/k_5$,
and $K'' = k_4k_4'/(2k_5k_3')^{\frac{1}{2}}$.

The values for the constants C', C'', $\frac{1}{2}nK'$, and nK'' which give the best agreement with experiment when substituted in equations (I) and (II) are:

$$C' = 2{\cdot}00 \times 10^{-4};\ C'' = 2{\cdot}56 + 10^{-4};\ \tfrac{1}{2}nK' = 8{\cdot}40 \times 10^{-4};\ nK'' = 2{\cdot}12 \times 10^{-4}.$$

The curves calculated from these equations are given in Figs. 1—4 for comparison with the experimental measurements.

From the above definitions of C' and K', we have

$$\tfrac{1}{2}nK'/C' = nk_4/k_5$$

From the values of $\frac{1}{2}nK'$ and of C' which give the best agreement with the experimental results when substituted in equations (I) and (II) we can obtain a value for the ratio nk_4/k_5. The results presented in Part II showed that there was only limited variation in the value of the ratio k_4/k_2 for a series of different olefins. If we assume that the ratio k_4/k_2 in the polymerisation of tetrafluoroethylene induced by acetaldehyde photolysis has the same value as that for the polymerisation of ethylene, we arrive at the value 26 for the number of tetrafluoroethylene molecules incorporated into each molecule of product. This is in general agreement with the melting point of the polymer, with the fact that C–H linkages (from the initiating methyl radicals) are still detectable by infra-red spectra, and with the *X*-ray diffraction data.

We express our thanks to Imperial Chemical Industries Limited, General Chemicals Division, for gifts of the fluorinated olefins, to Mr. C. W. Bunn for the *X*-ray diffraction study of the polymer, and to Professor Sir C. N. Hinshelwood for continual help and interest in this work.

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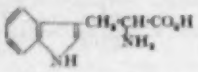
331. *Some Benziminazolylalanines.*

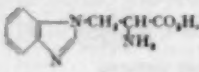
By P. Mamalis, V. Petrow, and B. Sturgeon.

Some *benziminazolylalanines* structurally related to the bacterial metabolite tryptophan (I) have been prepared by condensation of the appropriate *chloromethylbenziminazoles* with acetamidomalonic ester, followed by acid hydrolysis. Biological study of these compounds failed to reveal activity against a variety of organisms.

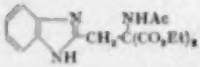
The concept that a substance structurally related to a metabolite may interfere with the function of that metabolite in living cells provides a unique starting point for the synthesis of biologically active compounds. Experimentally illustrated in the case of sulphanilamide and *p*-aminobenzoic acid (cf. Fildes, *Lancet*, 1940, **238**, 955), its application to the field of essential amino-acids has led to the preparation of bacterial inhibitors of quite remarkable activity.

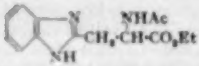
Tryptophan (I) is now largely accepted as an essential metabolite in bacterial species, whilst its analogues occasionally show competitive growth inhibition. Thus the *Bz*-methyltryptophans (Rydon, *J.*, 1948, 705) show varying degrees of activity against *Bacterium typhosum* 3390 (Fildes and Rydon, *Brit. J. Exp. Path.*, 1947, **28**, 211), and 5-methyltryptophan inhibits the growth of *B. coli* (Anderson, *Science*, 1945, **101**, 565). Apart from β-(3-thionaphthenyl)alanine • (Elliott and Harington, *J.*, 1949, 1374; Avakian, Moss, and Martin, *J. Amer. Chem. Soc.*, 1948, **70**, 3075), the preparation of heterocyclic types related to (I) has received scant attention. We now report the synthesis of some tryptophan analogues derived from benziminazole, a ring system shown in these laboratories to be present in vitamin B_{12} (Beavan, Holiday, Johnson, Ellis, Mamalis, Petrow, and Sturgeon, *J. Pharm. Pharmacol.*, 1949, **1**, 957).

(I.) 



(II.)

(III.) 



(IV.)

Treatment of 1-hydroxymethylbenziminazole with thionyl chloride gave *1-chloromethylbenziminazole hydrochloride* which condensed readily with ethyl acetamidomalonate in the presence of two moles of sodium ethoxide. As the resulting ester could not be isolated in a crystalline state, the product was directly hydrolysed yielding *β-(1-benziminazolyl)-α-alanine monohydrate* (II). The molecule of water in (II) was retained even after the substance had been dried *in vacuo*, and indeed hydration seemed a characteristic of this series of compounds. Accurate analytical data were thus difficult to obtain.

Attempts to extend the above reaction to the alkylbenziminazoles proved unsuccessful. 5-Methylbenziminazole gave what was apparently an inseparable mixture of 5- and 6-methyl-1-hydroxymethylbenziminazole when treated with formaldehyde in methanol. *5 : 6-Dimethyl-1-hydroxymethylbenziminazole* proved rather unstable, decomposing readily with liberation of formaldehyde, and no attempt was made to chlorinate it. 2-Methyl- and 2-ethyl-benziminazole failed to form 1-hydroxymethyl derivatives under these conditions (cf. Bachmann and Lovell, *J. Amer. Chem. Soc.*, 1946, **68**, 2496). The condensation of these two compounds with 1-acetamidoacrylic acid (cf. Adams and Johnson, *J. Amer. Chem. Soc.*, 1949, **71**, 705) appeared to offer an alternative approach, but, in dioxan, only the preferential polymerisation of the acrylic acid occurred. Addition of quinol inhibited the latter reaction but the required addition still failed to take place.

Condensation of 2-chloromethylbenziminazole or its hydrochloride with ethylacetamidomalonate and sodium ethoxide in boiling ethanol gave *ethyl acetamido-(2-benziminazolylmethyl)-malonate* (III) (65%), together with small quantities of a by-product, readily isolated from the reaction mixture by virtue of its insolubility in benzene. The by-product was identified as *ethyl α-acetamido-β-(2-benziminazolyl)propionate* (IV) by comparison with an authentic specimen prepared from the amino-acid (see below). *4-Methyl-*, *5-methyl-*, and *5 : 6-dimethyl-2-chloromethylbenziminazole hydrochloride*, under the same conditions, gave only the corresponding *acetamidopropionic esters* (cf. IV) in *ca.* 40% yields. Evidence for the formation of the malonic esters (cf. III) was obtained in the case of the 5-methyl isomer, but the

• The "β" in this name refers to the position of the substituent and the substance might be termed "β-(3-thionaphthenyl)-α-alanine." Ed.

material could not be obtained crystalline. *Ethyl acetamido-(1-methyl-2-benziminazolylmethyl)-malonate*, on the other hand, was the sole product of reaction between 1-methyl-2-chloromethylbenziminazole and the acetamidomalonic ester. Hydrolysis of these intermediates (types III and IV) with hydrobromic acid gave the corresponding amino-acids. β-(2-Benziminazolyl)-α-alanine and its 1-, 4-, and 5-methyl derivatives formed *monohydrates*, whilst β-(5 : 6-dimethyl-2-benziminazolyl)-α-alanine was obtained as the *dihydrate*.

Attempts to prepare α-amino-γ-(2-benziminazolyl)butyric acid by condensing *o*-phenylenediamine with glutamic acid were uniformly unsuccessful. *5-[2-(2-Benziminazolyl)ethyl]-hydantoin* was readily prepared by reaction of the diamine with β-(5-hydantoinyl)propionic acid in 4*N*-hydrochloric acid, but its subsequent conversion into the amino-acid could not be accomplished.

Inter alia preparation of 5 : 6-*dimethyl-2-benzamidomethylbenziminazole* was achieved by fusion of 4 : 5-dimethyl-*o*-phenylenediamine with hippuric acid and this substance furnished 5 : 6-*dimethyl-2-aminomethylbenziminazole dihydrochloride* on hydrolysis with concentrated hydrochloric acid. 2'-Phthalimidoethyl-*o*-phenylenediamine (Karrer and Naef, *Helv. Chim. Acta*, 1936, **19**, 1026) was converted into the *benziminazole* and thence, by hydrolysis with hydrazine, etc., into 1-(2-*aminoethyl*)*benziminazole dihydrochloride*.

Biological Results.—Dr. S. W. F. Underhill and his staff (Physiological Department, The British Drug Houses Ltd.,) have kindly examined β-(1-benziminazolyl)-, β-(2-benziminazolyl)-, and β-(5-methyl-2-benziminazolyl)-α-alanine hydrate for a variety of biological properties. The compounds failed to affect the growth of *Lactobacillus lactis* Dorner (experiments with Miss F. E. Larkin, B.Sc.). They showed negligible activity against a variety of Gram-positive and Gram-negative organisms, including *Mycobacterium tuberculosis* (experiments with Mr. J. T. Gunner). They were likewise inactive against *Trichomonas vaginalis* (experiments with Miss M. Cash, B.Sc.) and *Entamœba histolytica* (experiments with Mr. J. T. Gunner). β-(2-Benziminazolyl)-α-alanine hydrate had a low toxicity on intravenous administration to albino mice, but proved an irritant at the point of injection when administered either intravenously or subcutaneously. It appeared to have little action on the central nervous system (experiments with Miss J. M. Lesford, B.Sc.).

Experimental.

M. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss, Oxford. The benziminazolyl-α-alanines described below gave purple colours with a ninhydrin reagent in aqueous solution.

1-*Chloromethylbenziminazole Hydrochloride*.—1-Hydroxymethylbenziminazole (16 g.) (Bachmann and Lowell, *loc. cit.*) was added in portions to thionyl chloride (150 ml.), and the clear solution heated under reflux for about 1 hour. Evaporation *in vacuo* gave a yellow gum which crystallised on treatment with methanol. 1-*Chloromethylbenziminazole hydrochloride* (17 g.) separated from alcohol–benzene in needles, m. p. 173—174° (decomp.) (Found : N, 13·6. $C_8H_8N_2Cl_2$ requires N, 13·8%).

β-(1-*Benziminazolyl*)-α-*alanine Monohydrate*.—Sodium (2·3 g.) was dissolved in dry alcohol (150 ml.), and the coldsolution treated with ethyl acetamidomalonate (11·7 g.), followed by 1-chloromethylbenziminazole hydrochloride (10·8 g.). After 2 hours' boiling, the mixture, freed from salt, was evaporated to dryness under reduced pressure and the residual gum purified by passing a filtered benzene solution through a column of alumina. Evaporation of the eluate gave a yellow gum (10·7 g.) which was hydrolysed by boiling it with concentrated hydrobromic acid (150 ml.) for 4 hours. β-(1-*Benziminazolyl*)-α-*alanine dihydrobromide*, isolated by evaporation to dryness, separated from water–acetone in prisms, m. p. 192° (decomp.) (Found : Br, 43·0. $C_{10}H_{11}O_2N_3.2HBr$ requires Br, 43·7%). An aqueous solution of this hydrobromide was made faintly alkaline with potassium hydrogen carbonate and then adjusted to pH 6 with acetic acid. β-(1-*Benziminazolyl*)-α-*alanine monohydrate* separated and was recrystallised from water–alcohol, forming prisms (4·5 g.), m. p. 196° (with foaming) (Found : C, 53·3; H, 5·6; N, 19·0. $C_{10}H_{11}O_2N_3.H_2O$ requires C, 53·6; H, 5·8; N, 18·9%).

5- *and* 6-*Methyl-1-hydroxymethylbenziminazole*.—A solution of 5-methylbenziminazole (1·0 g.) in methanol (15 ml.) was treated with formaldehyde solution (1 ml. ; 40%) and set aside overnight. Concentration gave colourless needles, m. p. 137—140°, unchanged by further recrystallisation from methanol This was probably a mixture of 5- and 6-methyl-1-hydroxymethylbenziminazole (Found : N, 17·6. $C_9H_{10}ON_2$ requires N, 17·3%).

5 : 6-*Dimethyl-1-hydroxymethylbenziminazole* separated immediately on addition of formaldehyde to a methanolic solution of the base. It was purified by digestion with acetone and formed colourless prisms, m. p. 195—197° (decomp.) (Found : N, 16·2. $C_{10}H_{12}ON_2$ requires N, 15·9%).

2-*Hydroxymethylbenziminazoles*.—The appropriate *o*-phenylenediamine (0·1 mol.) was heated at 140—150° for 2 hours with 66% glycollic acid (0·2 mol.). The melt was triturated with dilute aqueous ammonia, and the product recrystallised from water containing a little alcohol (charcoal).

1-Methyl-2-hydroxymethylbenziminazole (70%) separated from benzene in colourless plates, m. p. 145° (Found : C, 66·2; H, 6·3; N, 17·1. Calc. for $C_9H_{10}ON_2$: C, 66·6; H, 6·2; N, 17·3%). This compound has previously been prepared by Hughes and Lions (*J. Proc. Roy. Soc., New South Wales*, 1938, **71**, 209) by methylation of 2-hydroxymethylbenziminazole.

4-*Methyl-2-hydroxymethylbenziminazole* formed silver platelets (75%), m. p. 198°, from water (Found : C, 66·2; H, 6·3; N, 17·4%).

5-Methyl-2-hydroxymethylbenziminazole crystallised in silver platelets (76%), m. p. 202—203°, from water containing a little alcohol (Found: C, 66·7; H, 6·3; N, 17·0%).

5 : 6-Dimethyl-2-hydroxymethylbenziminazole (55%) formed leaflets (from alcohol), m. p. 253—254° (Found: N, 15·6%).

2-Chloromethylbenziminazoles.—The 2-hydroxymethylbenziminazoles were chlorinated in the manner described for 1-hydroxymethylbenziminazole.

2-Chloromethylbenziminazole hydrochloride (80%) crystallised from methanol–ethyl acetate in yellow needles, m. p. 229° (decomp.) (Found: N, 13·9; Cl, 34·5. $C_8H_8N_2Cl_2$ requires N, 13·8; Cl, 35·0%). The free chloro-compound separated from aqueous alcohol in fine needles, m. p. 159° (Found: N, 17·0; Cl, 21·3. Calc. for $C_8H_7N_2Cl$: N, 16·8; Cl, 21·3%). Bloom and Day (*J. Org. Chem.*, 1939, **4**, 14) record the m. p. as 161°.

1-Methyl-2-chloromethylbenziminazole (85%) separated from light petroleum (b. p. 60—80°) in long needles, m. p. 96° (Found: N, 15·6; Cl, 19·8. Calc. for $C_9H_9N_2Cl$: N, 15·5; Cl, 19·6%). Hughes and Lions (*loc. cit.*) give m. p. 94°.

4-Methyl-2-chloromethylbenziminazole hydrochloride separated (80%) from alcohol–benzene in platelets, m. p. 251—252° (decomp.) (Found: N, 12·8; Cl, 32·2. $C_9H_{10}N_2Cl_2$ requires N, 12·9; Cl, 32·7%).

5-Methyl-2-chloromethylbenziminazole hydrochloride (75%) formed felted needles, m. p. 216° (decomp.), from alcohol–benzene (Found: N, 13·0; Cl, 32·1%).

5 : 6-Dimethyl-2-chloromethylbenziminazole hydrochloride (70%) crystallised from methanol–ethyl acetate in buff-coloured prisms, m. p. 282° (decomp.) (Found: N, 12·1. $C_{10}H_{12}N_2Cl_2$ requires N, 12·1%).

Condensation of 2-Chloromethylbenziminazole with Ethyl Acetamidomalonate.—2-Chloromethylbenziminazole (12·3 g.) and ethyl acetamidomalonate (16 g.) were condensed in dry ethanol (150 ml.) containing sodium ethoxide (from 1·7 g. of sodium) by the standard procedure. The product was extracted with boiling benzene (300 ml.), and the insoluble material (1·5 g.) recrystallised from alcohol–benzene to give *ethyl α-acetamido-β-(2-benziminazolyl)propionate* (IV) in fine needles, m. p. 214° (Found: C, 60·6; H, 5·9; N, 15·1. $C_{14}H_{17}O_3N_3$ requires C, 61·1; H, 6·2; N, 15·2%), not depressed on admixture with a specimen prepared as below. The benzene solution was chromatographed on a column of alumina (4 × 50 cm.), and the column washed with benzene–ethyl acetate (1 : 1; 500 ml.). Evaporation of the eluate gave a yellow gum which crystallised on treatment with a little ethyl acetate. *Ethyl acetamido-(2-benziminazolylmethyl)malonate* (17 g., 65%) separated from benzene–light petroleum in rhombs, m. p. 162—163° (Found: C, 58·3; H, 5·9; N, 12·3. $C_{17}H_{21}O_5N_3$ requires C, 58·8; H, 6·0; N, 12·1%). Condensation of 2-chloromethylbenziminazole hydrochloride with ethyl acetamidomalonate in the presence of 2 mols. of sodium ethoxide gave essentially the same result.

β-(2-Benziminazolyl)-α-alanine Monohydrate.—Hydrolysis of either of the foregoing intermediates with concentrated hydrobromic acid, followed by isolation in the manner described above for the isomeric amino-acid, gave β-(2-benziminazolyl)-α-alanine as the *monohydrate* which crystallised from water–alcohol in fine white needles, m. p. 210° (with foaming) (Found: C, 54·2; H, 5·9; N, 18·5. $C_{10}H_{11}O_2N_3.H_2O$ requires C, 53·8; H, 5·8; N, 18·9%). The *hydrobromide* formed colourless crystals (from water–acetone), m. p. 237° (decomp.) (Found: N, 14·7; Br, 28·0. $C_{10}H_{11}O_2N_3.HBr$ requires N, 14·8; Br, 28·2%).

Ethyl α-Acetamido-β-(2-benziminazolyl)propionate.—Dry hydrogen chloride was passed into a suspension of the amino-acid (1·4 g.) in boiling absolute ethanol (50 ml.) for 1 hour, whereafter the solution was evaporated to dryness. The residue was warmed with acetic anhydride (20 ml.) for 1 hour and the excess then removed under reduced pressure. Crystallisation of the residue from aqueous alcohol containing a little ammonia and then from alcohol–light petroleum gave *ethyl α-acetamido-β-(2-benziminazolyl)propionate*, colourless needles (500 mg.), m. p. 216° (Found: C, 61·0; H, 6·0; N, 15·2. $C_{14}H_{17}O_3N_3$ requires C, 61·1; H, 6·2; N, 15·2%), not depressed on admixture with a specimen prepared as above.

Ethyl acetamido-(1-methyl-2-benziminazolylmethyl)malonate, prepared from 1-methyl-2-chloromethyl benziminazole (6·9 g.), ethyl acetamidomalonate (8·4 g.), and dry alcohol (100 ml.), containing sodium (0·85 g.), separated from light petroleum (b. p. 80—100°) containing a little benzene in fine needles (9·0 g.), m. p. 133—134° (Found: C, 59·7; H, 6·2; N, 12·0. $C_{18}H_{23}O_5N_3$ requires C, 59·8; H, 6·4; N, 11·6%).

β-(1-Methyl-2-benziminazolyl)-α-alanine monohydrate was obtained as a gel by hydrolysis of the foregoing ester. On drying *in vacuo* over phosphoric oxide, it formed a friable white powder, m. p. *ca.* 216—219° (with foaming) (Found: C, 54·8; H, 6·0; N, 17·4. $C_{11}H_{13}O_2N_3.H_2O$ requires C, 55·7; H, 6·2; N, 17·8%).

β-(4-Methyl-2-benziminazolyl)-α-alanine Monohydrate.—4-Chloromethylbenziminazole hydrochloride (7·7 g.) and ethyl acetamidomalonate (8·5 g.) were condensed in boiling ethanol (120 ml.) containing sodium (1·75 g.). The reaction product in benzene (100 ml.) was chromatographed on a column of alumina (3·5 × 25 cm.), and the column washed with benzene (300 ml.) containing 10% of ethanol. Evaporation of the eluate gave a reddish gum which crystallised on treatment with ethyl acetate. *Ethyl α-acetamido-β-(4-methyl-2-benziminazolyl)propionate* (4 g., 40%) separated from alcohol–light petroleum in needles, m. p. 172° (Found: C, 62·4; H, 6·7; N, 14·4. $C_{15}H_{19}O_3N_3$ requires C, 62·3; H, 6·6; N, 14·5%). Hydrolysis gave *β-(4-methyl-2-benziminazolyl)-α-alanine monohydrate*, needles (from water), m. p. 210° (with foaming) (Found: C, 56·2; H, 6·5; N, 18·2. $C_{11}H_{13}O_2N_3.H_2O$ requires C, 55·7; H, 6·2; N, 17·8%).

β-(5-Methyl-2-benziminazolyl)-α-alanine Monohydrate.—5-Methyl-2-chloromethylbenziminazole hydrochloride (6·0 g.) was condensed with ethyl acetamidomalonate (7·5 g.) in dry ethanol (120 ml.) containing sodium ethoxide (2 mols.). The crude product was stirred with benzene giving *ethyl α-acetamido-β-(5-methyl-2-benziminazolyl)propionate* (3·9 g., 50%), colourless needles (from alcohol–benzene), m. p. 209° (Found: C, 62·2; H, 6·7; N, 14·6%). The benzene-soluble fraction was not obtained crystalline, even after repeated chromatographic purification. On hydrolysis with concentrated hydrobromic acid it gave β-(5-methyl-2-benziminazolyl)-α-alanine, also obtained by hydrolysis of the acetamidopropionic ester. This compound, isolated as the *monohydrate*, formed colourless needles, m. p. 196° (with foaming), from water (Found: C, 56·6; H, 6·4; N, 17·7%). The *hydrobromide* separated from water–acetone

in colourless crystals, m. p. 245° (decomp.) (Found: N, 13·6. $C_{11}H_{13}O_3N_3$,HBr requires N, 14·0%), and the *picrate* in yellow needles, m. p. 208° (decomp.) (Found: N, 15·6. $C_{11}H_{13}O_3N_3$,$C_6H_3O_7N_3$ requires N, 15·8%), from alcohol.

β-(5 : 6-Dimethyl-2-benziminazolyl)-α-alanine Dihydrate.—Condensation of 5 : 6-dimethyl-2-chloromethylbenziminazole hydrochloride (5·8 g.) with ethyl acetamidomalonate (5·2 g.) gave *ethyl α-acetamido-β-(5 : 6-dimethyl-2-benziminazolyl)propionate*, colourless needles (from alcohol–light petroleum), m. p. 182°, which appeared to retain a molecule of ethanol after drying at 78°/100 mm. (Found: C, 61·2; H, 6·8; N, 12·1. $C_{16}H_{21}O_3N_3$,C_2H_5·OH requires C, 61·6; H, 7·3; N, 12·0%). Hydrolysis gave *β-(5 : 6-dimethyl-2-benziminazolyl)-α-alanine* which separated from water containing a little acetic acid as the *dihydrate*, m. p. 210° (with foaming) (Found: C, 53·8; H, 7·1; N, 15·2. $C_{13}H_{15}O_2N_3$,$2H_2O$ requires C, 53·8; H, 7·1; N, 15·7%).

5-[2-(2-Benziminazolyl)ethyl]hydantoin.—*β-(5-Hydantoinyl)propionic acid* (4 g.; Dakin, *Biochem. J.*, 1919, **13**, 406) and *o*-phenylenediamine (2 g.) were heated under reflux in 4*N*-hydrochloric acid (20 ml.) for 1 hour. The *product* separated on basification with aqueous ammonia, and was recrystallised from water (charcoal), forming fine needles, m. p. 247—248° (decomp.) (Found: C, 58·7; H, 4·9; N, 22·6. $C_{13}H_{12}O_2N_4$ requires C, 59·0; H, 4·9; N, 22·9%).

1-(2-Hydroxyethyl)benziminazole.—2-Nitro-2′-hydroxyethylaniline (6·1 g.) was reduced in alcoholic solution when shaken with hydrogen in the presence of palladised charcoal. The diamine was transferred to 4*N*-hydrochloric acid (40 ml.) and heated at 100° with formic acid (15 ml.) for 40 minutes, whereafter the product was precipitated with ammonia solution and extracted with chloroform. 1-(2-Hydroxyethyl)benziminazole (5·8 g., 75%) formed colourless needles, m. p. 108°, from benzene. The picrate formed long yellow needles (from 2-ethoxyethanol), m. p. 205° (Found: N, 17·6. Calc. for $C_9H_{10}ON_2$,$C_6H_3O_7N_3$: N, 17·9%).

2-Methyl-1-(2-hydroxyethyl)benziminazole.—This *benziminazole* was prepared as above, the formic acid being replaced by acetic acid, and separated (65%) from ethyl acetate–light petroleum in prisms, m. p. 148° (Found: C, 68·4; H, 6·9; N, 15·9. $C_{10}H_{12}ON_2$ requires C, 68·2; H, 6·9; N, 15·9%).

2-Ethyl-1-(2-hydroxyethyl)benziminazole formed prismatic needles (70%), m. p. 133°, from aqueous alcohol (Found: N, 14·7. $C_{11}H_{14}ON_2$ requires N, 14·7%).

5 : 6-Dimethyl-2-aminomethylbenziminazole Dihydrochloride.—4 : 5-Dimethyl-*o*-phenylenediamine (from the catalytic reduction of 4·15 g. of 5-nitro-*o*-4-xylidine) and hippuric acid (4·6 g.) were fused at 170° for 15 minutes. The product was ground and then recrystallised from aqueous alcohol, giving *5 : 6-dimethyl-2-benzamidomethylbenziminazole* in wisps, m. p. 233—234° (Found: C, 68·9; H, 6·6. $C_{17}H_{17}ON_3$,H_2O requires C, 68·7; H, 6·4%). This compound (2·1 g.) was heated under reflux for 8 hours with concentrated hydrochloric acid, whereafter the solution was evaporated to dryness. Benzoic acid was removed by extraction with ether and the residue recrystallised from alcohol–ether. *5 : 6-Dimethyl-2-aminomethylbenziminazole dihydrochloride* formed needles (900 mg.), m. p. 266—268° (Found: N, 16·9. $C_{10}H_{13}N_3$,$2HCl$ requires N, 17·3%).

1-(2-Aminoethyl)benziminazole.—2′-Phthalimidoethyl-*o*-phenylenediamine (3 g.; Karrer and Naef, *Helv. Chim. Acta*, 1936, **19**, 1026) and 95% formic acid (12 ml.) were heated under reflux for 1 hour. On basification with aqueous ammonia, *1-(2-phthalimidoethyl)benziminazole* (80%) separated and was recrystallised from alcohol, forming prisms, m. p. 211° (Found: N, 14·1. $C_{17}H_{13}O_2N_3$ requires N, 14·4%). This intermediate (2·5 g.) and hydrazine hydrate (25 ml.) were heated under reflux for 2 hours. The solution was evaporated, and the residue treated with dilute hydrochloric acid and filtered from phthalhydrazide. *1-(2-Aminoethyl)benziminazole dihydrochloride* (750 mg.) was isolated from the filtrate by evaporation to dryness and was recrystallised from alcohol, forming needles, m. p. 280° (Found: C, 46·6; H, 5·5; N, 17·8; Cl, 30·6. $C_9H_{11}N_3$,$2HCl$ requires C, 46·2; H, 5·6; N, 18·0; Cl, 30·3%).

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Research Laboratories,
The British Drug Houses Ltd., London, N.1. [*Received, February 22nd*, 1950.]

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332. *Contributions to the Chemistry of Synthetic Antimalarials. Part IX. Some Pyrimidine Derivatives.*

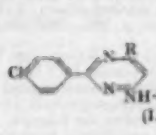
By J. S. Moffatt.

The syntheses of 4-(4-diethylamino-1-methylbutylamino)-2-*p*-chlorophenylpyrimidine and certain of its chloro-, amino-, and methoxy-derivatives are described. Of these, only the first mentioned has been found to show some activity against *Plasmodium gallinaceum*.

This work was initiated in continuation of a project to prepare and examine for antimalarial activity alkylaminoalkylamino-derivatives of simple heterocyclic systems (cf. Part I, Ashley and Grove, *J.*, 1945, 768). The pyrimidine ring was chosen since, at the time this work was begun, it did not appear to have received attention in previous antimalarial investigations although its biological importance was well known. Moreover, the amidine grouping, which may be considered to form part of the pyrimidine ring, is present in certain aromatic diamidines such as 1 : 5-di-*p*-amidinophenoxypentane (Pentamidine) which show some chemotherapeutic

activity in experimental malaria (Fulton, *Ann. Trop. Med. and Parasitol.*, 1940, **34**, 53; Yorke, *Trans. Roy. Soc. Trop. Med. and Hygiene*, 1940, **33**, 463). Considerations which led to the study first of derivatives of 2-*p*-chlorophenylpyrimidine were: (i) 2-arylpyrimidines appeared to be among the more readily accessible of pyrimidine derivatives and therefore one of the objectives of this work became the preparation of (I; R = OMe) which is of the same order of molecular complexity, and contains the same basic side-chain, and chloro- and methoxy-substituents as Mepacrine; (ii) it has been found in these laboratories (Moffatt, unpublished observation) that introducing a *p*-chlorophenyl group into one of the amidine groups of 1 : 3-di-*p*-amidinophenoxypropane (Propamidine) enhances the slight antimalarial activity of the diamidine. During the course of the preliminary work described below, a number of derivatives of 2-alkylaminoalkylamino- and 2-amino-4-alkylaminoalkylamino-pyrimidine were described by Adams and Whitmore (*J. Amer. Chem. Soc.*, 1945, **67**, 735, 1159), and shortly after it was completed, the author learned (Curd and Rose, Scientific Meeting, Chemical Society, February 7th, 1946) of the series of comprehensive researches, which had been initiated by Curd, Rose, *et al.* (see *J.*, 1946, 343 and subsequent papers), on alkylaminoalkylaminopyrimidine derivatives. Accordingly, further work along similar lines was abandoned. It is now apparent that the preparation of the pyrimidine derivatives described in the present work was not undertaken by these authors or their collaborators, and therefore the syntheses are now recorded.

p-Chlorobenzamidine was condensed with ethyl malonate in presence of excess of sodium ethoxide (cf. Dox and Yoder, *J. Amer. Chem. Soc.*, 1922, **44**, 361) to give 4 : 6-dihydroxy-2-*p*-chlorophenylpyrimidine which was converted, by Baddiley and Topham's method (*J.*, 1944, 678), into 4 : 6-dichloro-2-*p*-chlorophenylpyrimidine. Use was made of the oft-observed fact (see *e.g.* Buttner, *Ber.*, 1903, **36**, 2227) that the chlorine atoms in 4 : 6-dichloropyrimidines, by choice of conditions, may stepwise be made to react with reagents such as sodium methoxide and amines. Thus, 4 : 6-dichloro-2-*p*-chlorophenylpyrimidine with 4-diethylamino-1-methylbutylamine at 80—90° gave 4-chloro-6-(4-diethylamino-1-methylbutylamino)-2-*p*-chlorophenylpyrimidine (I; R = Cl). A large excess of the aliphatic diamine and a temperature of



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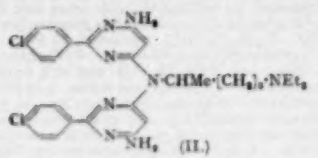

(II.)

ca. 210° gave 4 : 6-di-(4-diethylamino-1-methylbutylamino)-2-*p*-chlorophenylpyrimidine (I; R = NH·CHMe·[CH$_2$]$_3$·NEt$_2$). With ethanolic ammonia at 125—130° and one equivalent of sodium methoxide in boiling methanol the 4 : 6-dichloropyrimidine afforded, respectively, 4-chloro-6-amino- and 4-chloro-6-methoxy-2-*p*-chlorophenylpyrimidine. With 4-diethylamino-1-methylbutylamine at 200°, the former yielded 4-amino-6-(4-diethylamino-1-methylbutylamino)- (I; R = NH$_2$) and the latter 4-(4-diethylamino-1-methylbutylamino)-6-methoxy-2-*p*-chlorophenylpyrimidine (I; R = OMe). These were accompanied by small quantities of by-products; in the case of the former condensation, the by-product was identified as 4-diethylamino-*NN*-di-(4-amino-2-*p*-chlorophenyl-6-pyrimidyl)-1-methylbutylamine (II). For the preparation of 4-(4-diethylamino-1-methylbutylamino)-2-*p*-chlorophenylpyrimidine (I; R = H), it was considered desirable to start from the appropriate monohydroxy-pyrimidine in order to avoid the ambiguity which might arise from removal of one chlorine atom from the corresponding 6-chloro-derivative of 4-(4-diethylamino-1-methylbutylamino)-2-*p*-chlorophenylpyrimidine (I; R = Cl). This appeared to be accessible by application of the method of Gabriel (*Ber.*, 1904, **37**, 3638), who obtained 4-hydroxy-2-methylpyrimidine by interaction of approximately equimolecular proportions of acetamidine hydrochloride and ethyl sodioformylacetate. However, interaction of similar proportions of the latter and *p*-chlorobenzamidine hydrochloride yielded a substance, $C_{11}H_{14}ON_2Cl_2$, which, on being heated at its m. p., decomposed to give ammonia, *p*-chlorobenzonitrile, and 4-hydroxy-2-*p*-chlorophenylpyrimidine. The hydroxypyrimidine was the principal product of the interaction of equimolecular amounts of *p*-chlorobenzamidine and ethyl sodioformylacetate. It was converted into 4-chloro-2-*p*-chlorophenylpyrimidine which, with 4-diethylamino-1-methylbutylamine at 190°, yielded 4-(4-diethylamino-1-methylbutylamino)-2-*p*-chlorophenylpyrimidine (I; R = H).

Each of the compounds (I; R = H), (I; R = Cl), (I; R = NH$_2$), (I; R = OMe), and

(I; R = NH·CHMe·[CH_2]$_3$·NEt_2) was examined against *P. gallinaceum* in chicks, but only (I; R = H) showed any activity, and then only of a low order.

Experimental.

4 : 6-*Dihydroxy*-2-p-*chlorophenylpyrimidine*.—A solution of sodium (13·5 g.) in anhydrous ethanol (225 c.c.) was gradually treated with *p*-chlorobenzamidine hydrochloride (Ekeley, Tiessen, and Rosazio, *J. Amer. Chem. Soc.*, 1935, **57**, 381) (33 g.), followed by ethyl malonate (25·5 g.). The mixture was heated under reflux on a water-bath for 5 hours, and then distilled from the water-bath to remove ethanol. The residual solid was treated with water (600 c.c.), and the resulting solution was filtered from a small quantity of insoluble material. Acidification of the filtrate with acetic acid gave the *dihydroxy-pyrimidine* [29·8 g.; m. p. 308—311° (decomp.)], which was sufficiently pure for the next stage. A sample separated from glacial acetic acid in sheaves of thick needles, m. p. 320—327° (decomp.) (Found : N, 12·3; Cl, 15·7. $C_{10}H_7O_2N_2Cl$ requires N, 12·6; Cl, 15·9%).

4 : 6-*Dichloro*-2-p-*chlorophenylpyrimidine*.—A mixture of the dihydroxypyrimidine (25 g.) and phosphoryl chloride (125 c.c.) was cautiously treated with dimethylaniline (28 c.c.). The resulting solution was boiled under reflux for 2·5 hours, cooled, and then poured on crushed ice. The precipitate, on crystallisation from ethanol, formed clusters of colourless needles (24·5 g.) of the 4 : 6-*dichloro-pyrimidine*, m. p. 123° (Found : N, 10·6; Cl, 41·0. $C_{10}H_5N_2Cl_3$ requires N, 10·8; Cl, 41·0%).

4-*Chloro*-6-(4-*diethylamino*-1-*methylbutylamino*)-2-p-*chlorophenylpyrimidine*.—The foregoing chloro-compound (3 g.) was heated under reflux with a mixture of 4-diethylamino-1-methylbutylamine (5 c.c.) and ethanol (15 c.c.) in an oil-bath at 100—105°, for 3 hours. Most of the solvent was then allowed to distil off, and the residue was treated with water and ether. The ethereal layer was washed several times with water, and the solvent then evaporated. The residual *base* distilled at 195—200°/0·05 mm. (bath temp.), as a viscous, yellow oil (4·1 g.) (Found : N, 14·7; Cl, 18·6. $C_{19}H_{27}N_4Cl_2$ requires N, 14·7; Cl, 18·6%). It gave a *monopicrate* which formed orange rhombs (from ethanol), m. p. 158° (Found : C, 49·4; H, 4·5; N, 15·9. $C_{19}H_{27}N_4Cl_2C_6H_3O_7N_3$ requires C, 49·2; H, 4·8; N, 16·1%).

4 : 6-*Di*-(4-*diethylamino*-1-*methylbutylamino*)-2-p-*chlorophenylpyrimidine*.—4 : 6-Dichloro-2-*p*-chlorophenylpyrimidine (3 g.) was heated with a mixture of 4-diethylamino-1-methylbutylamine (14·6 g.) and anhydrous methanol (12 c.c.) at 200—210° for 5 hours in a sealed tube. The reaction mixture was concentrated on a water-bath, and the residue treated with water and ether. The ethereal solution was washed several times with water and the solvent then evaporated. The residue was fractionally distilled under reduced pressure, and the fraction (5·1 g.) which distilled at 205—220°/0·02 mm. (bath temp.) was collected. This was extracted with 0·5*N*-hydrochloric acid, and the extract was filtered, extracted twice with ether, and then made alkaline with dilute sodium hydroxide solution. The *base* which separated distilled at 222—230°/0·01 mm. (bath temp.) as a pale yellow oil (4·9 g.), which became very viscous on cooling (Found : C, 67·4; H, 9·2; Cl, 7·9. $C_{33}H_{61}N_6Cl$ requires C, 66·9; H, 9·4; Cl, 7·1%). Its *dipicrate* separated from ethanol in minute, glittering rhombs, m. p. 195—197° (Found : C, 49·0; H, 5·2; N, 17·4. $C_{33}H_{61}N_6Cl,2C_6H_3O_7N_3$ requires C, 49·9; H, 5·4; N, 17·5%).

4-*Chloro*-6-*amino*-2-p-*chlorophenylpyrimidine*.—A mixture of 4 : 6-dichloro-2-*p*-chlorophenylpyrimidine (5 g.) and anhydrous ethanol (30 c.c.) saturated with ammonia was heated at 125—128° for 3 hours in a sealed tube. The reaction mixture was concentrated on a water-bath; the residue was triturated with water, filtered off, and then repeatedly recrystallised from ethanol to give the *amine* as needles (3 g.), m. p. 190° (Found : N, 17·1; Cl, 30·0. $C_{10}H_7N_3Cl_2$ requires N, 17·5; Cl, 29·6%).

4-*Amino*-6-(4-*diethylamino*-1-*methylbutylamino*)-2-p-*chlorophenylpyrimidine*.—The 4-chloro-6-amino-pyrimidine (2·8 g.) was heated with 4-diethylamino-1-methylbutylamine (5 c.c.) and anhydrous methanol (15 c.c.) for 3 hours at 205—210° in a sealed tube. The crude product distilled at 202—212°/0·05 mm. (bath temp.). It was extracted with 0·5*N*-hydrochloric acid. The insoluble residue, on treatment with ethanol followed by repeated recrystallisation from the same solvent, formed needles (80 mg.) m. p. 157—158°, of 4-*diethylamino*-NN-*di*-(4-*amino*-2-p-*chlorophenyl*-6-*pyrimidyl*)-1-*methylbutylamine* (II) (Found : C, 61·7; H, 5·9; N, 19·6; Cl, 12·6. $C_{28}H_{34}N_8Cl_2$ requires C, 61·6; H, 6·0; N, 19·8; Cl, 12·6%). The aqueous acid extract was made alkaline with dilute sodium hydroxide; the resulting 4-*amino*-6-(4-*diethylamino*-1-*methylbutylamino*)-2-p-*chlorophenylpyrimidine* distilled at 204—212°/0·05 mm. (bath temp.) and formed a viscous, fluorescent oil (2·8 g.), which set to a clear, green glass on cooling (Found : C, 63·0; H, 7·2; N, 19·6; Cl, 10·8. $C_{19}H_{29}N_5Cl$ requires C, 63·1; H, 7·7; N, 19·4; Cl, 9·9%). The *dipicrate*, crystallised from ethanol, had m. p. 155—156° (Found : C, 45·9; H, 4·4; N, 15·8. $C_{19}H_{29}N_5Cl,2C_6H_3O_7N_3$ requires C, 45·4; H, 4·2; N, 15·8%).

4-*Chloro*-6-*methoxy*-2-p-*chlorophenylpyrimidine*.—A suspension of 4 : 6-dichloro-2-*p*-chlorophenyl-pyrimidine (5 g.) in methanol (150 c.c.) was boiled under reflux and treated dropwise, during 15 minutes, with a solution of sodium (0·44 g.) in methanol (10 c.c.). The mixture was boiled under reflux for one hour and then concentrated to a small bulk. The *chloromethoxy*-compound, which crystallised out, was filtered off, washed with water, and recrystallised from methanol to give needles (3·4 g.), m. p. 95—96° [Found : N, 10·9; OMe, 12·5. $C_{11}H_9N_2Cl_3$(OMe) requires N, 11·0; OMe, 12·2%].

4-(4-*Diethylamino*-1-*methylbutylamino*)-6-*methoxy*-2-p-*chlorophenylpyrimidine*.—The chloromethoxy-compound (3·5 g.) was heated with 4-diethylamino-1-methylbutylamine (6 c.c.) and anhydrous methanol (20 c.c.) at 200—205° for 3 hours in a sealed tube. Isolated in the usual manner and purified by extraction with 0·5*N*-hydrochloric acid, the *base* distilled at 175—185°/0·05 mm. (bath temp.) as a viscous yellow oil (2 g.) [Found : N, 15·1; OMe, 8·4. $C_{19}H_{29}N_4Cl$(OMe) requires N, 14·9; OMe, 8·2%]. Its *dipicrate* formed yellow needles (from ethanol), m. p. 146—147° (Found : C, 46·0; H, 4·4; *N*, 16·9. $C_{20}H_{29}ON_4Cl,2C_6H_3O_7N_3$ requires C, 46·0; H, 4·2; *N*, 16·8%).

The Reaction of p-*Chlorobenzamidine Hydrochloride with Ethyl Sodioformylacetate*.—A solution of the amidine hydrochloride (3·82 g.) in warm anhydrous ethanol (25 c.c.) was treated with ethyl sodioformyl-acetate (Gabriel, *loc. cit.*) (2·75 g.). The mixture was heated under reflux on a water-bath for 3 hours

and then filtered hot to remove sodium chloride. The solid (2·3 g.) which separated from the filtrate was collected, washed with water, and recrystallised from ethanol to give crystals, m. p. 131—134° (decomp.), of a substance (Found, on material dried in a vacuum desiccator: N, 13·8%) which, on being heated at 100°/12 mm. for 9 hours, lost 11·8% of its weight and gave the solvent-free *substance*, m. p. 199—200° (decomp.) (Found: C, 56·6; H, 4·1; N, 15·3. $C_{17}H_{14}ON_2Cl_2$ requires C, 56·5; H, 3·9; N, 15·5%. $C_{17}H_{14}ON_2Cl_2,C_2H_4O$ requires N, 13·9; loss in weight 11·3%). The latter (135 mg.), on being heated at 190—200° for one hour, gradually decomposed. Ammonia was evolved and white needles (40 mg.) of *p*-chlorobenzonitrile sublimed from the mixture. The non-volatile residue, on crystallisation from ethanol, yielded needles (60 mg.), m. p. 244—245°, of *4-hydroxy-2-p-chlorophenylpyrimidine* (Found: C, 58·0; H, 3·6; N, 13·4. $C_{10}H_7ON_2Cl$ requires C, 58·1; H, 3·4; N, 13·6%).

The Reaction of p-*Chlorobenzamidine with Ethyl Sodioformylacetate.*—A solution of sodium (1·38 g.) in ethanol (60 c.c.) was treated with *p*-chlorobenzamidine hydrochloride (11·5 g.). The mixture was shaken and warmed gently until separation of sodium chloride was complete. It was then treated with ethyl sodioformylacetate (8·28 g.), heated under reflux on a water-bath for 5·5 hours, and then set aside for 12 hours. The residue left on concentration of the mixture on the water-bath was treated with water (80 c.c.), and the solution filtered from a small quantity of gelatinous material. The filtrate, on being kept, deposited orange plates (2·0 g.), which, on recrystallisation from ethanol, yielded large rhombs, m. p. 145—148° (decomp.), of *p-chlorobenzamidine monohydrate* (Found: N, 16·3. $C_7H_7N_2Cl,H_2O$ requires N, 16·2%) which, with ethanolic hydrogen chloride, yielded *p*-chlorobenzamidine hydrochloride. The aqueous filtrate, when acidified with 50% acetic acid, gave a precipitate (6·8 g.), which was separated by fractional crystallisation from ethanol into *p*-chlorobenzamidine monohydrate (1·0 g.) as the more soluble product, and, as the less soluble product, needles (4·4 g.) of 4-hydroxy-2-*p*-chlorophenylpyrimidine.

4-Chloro-2-p-chlorophenylpyrimidine.—4-Hydroxy-2-*p*-chlorophenylpyrimidine (4·5 g.) was boiled under reflux for 2·5 hours with phosphoryl chloride (22 c.c.) and dimethylaniline (5 c.c.). The *chloro*-compound (3·4 g.) was sublimed at 100°/0·04 mm. and then recrystallised from ethanol to give plates, m. p. 121—122° (Found: N, 12·0; Cl, 31·8. $C_{10}H_6N_2Cl_2$ requires N, 12·5; Cl, 31·5%).

4-(4-Diethylamino-1-methylbutylamino)-2-p-chlorophenylpyrimidine.—The chloro-compound (2·25 g.) was heated with 4-diethylamino-1-methylbutylamine (6·3 g.) and anhydrous methanol (8 c.c.) at 185—190° for 4·5 hours in a sealed tube. The *base* distilled as a colourless oil (3 g.) at 175—184°/0·01 mm. (bath temp.) (Found: C, 65·7; H, 7·6; N, 16·2. $C_{19}H_{31}N_4Cl$ requires C, 65·8; H, 7·8; N, 16·2%). Its *dipicrate* separated from acetone–ether in yellow needles, m. p. 171—173° (Found: C, 46·3; H, 4·2; N, 17·2. $C_{19}H_{31}N_4Cl,2C_6H_3O_7N_3$ requires C, 46·2; H, 4·1; N, 17·4%).

The author is glad to acknowledge his indebtedness to Dr. A. J. Ewins, F.R.S., for his interest in this work, to Dr. R. Wien and his assistants for the biological data, to Mr. S. Bance, B.Sc., A.R.I.C., for the various semi-microanalyses, and to the Directors of May and Baker Ltd. for permission to publish these results.

Research Laboratories, May and Baker Ltd.,
Dagenham.

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333. *Alkaloids of* Daphnandra *Species. Part III. Micranthine.*

By I. R. C. Bick and A. R. Todd.

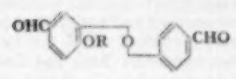
Micranthine, obtained as the sole alkaloidal constituent of a specimen of the bark of *D. micrantha* grown in Queensland, has a molecular formula $C_{18}H_{20}O_4N_2$ and contains one methoxy- and one methylimino-group. By a combination of degradative studies and consideration of biogenetic possibilities, it is concluded that the alkaloid has structure (VI) in which R_3 = H, of R_1 and R_2 one is H and the other Me, and of R_3 and R_4 one is H and the other Me. Micranthine is thus to be regarded as one of the small group of bisbenzylisoquinoline alkaloids containing a phenodioxin system, the other members being trilobine and *iso*trilobine [(VII) and (VIII)], menisarine, for which structure [(X) or (XI)] is preferred, and normenisarine. In agreement with the structures proposed for micranthine and menisarine, *N*-methyldihydromenisarinemethine and *OON*-trimethylmicranthinemethine (XII) appear to be identical, whilst *N*-methyldihydromenisarine is the enantiomorph of *OON*-trimethylmicranthine.

The alkaloid micranthine was first described by Pyman (*J.*, 1914, 1619) as a minor constituent of the bark of the Australian tree *Daphnandra micrantha*, where it was accompanied by much larger amounts of the alkaloids daphnandrine and daphnoline. As reported in Part II of this series (Bick, Ewen, and Todd, *J.*, 1949, 2767), we were unable to detect either of the last two alkaloids in a sample of *D. micrantha* bark collected in southern Queensland; this bark, however, contained micranthine in much larger quantity than Pyman's material. The bark used by Pyman appears to have been collected in New South Wales and there is some reason to believe that local botanical variation occurs within the species; this matter will be discussed in a later report.

Using an improved isolation procedure, micranthine, identical with the alkaloid described by Pyman (*loc. cit.*), was obtained in a yield of *ca.* 2%. Analysis showed that it contained one

methoxy- and one methylimino-group, and indicated a formula $C_{34}H_{32}O_6N_2$ rather than the $C_{34}H_{32}O_4N_2$ proposed by Pyman (*loc. cit.*). Tests for methylenedioxy-groups gave negative results, but with a mixture of nitric and sulphuric acids the alkaloid gave a blue coloration. Parallel tests showed that the colour was apparently identical with that given under similar conditions by trilobine (Tomita and Tani, *J. Pharm. Soc. Japan*, 1942, **62**, 94; Tani, *ibid.*, p. 146) and menisarine (Kondo and Tomita, *Arch. Pharm.*, 1936, **274**, 73), alkaloids of the Far Eastern menispermaceous plants *Cocculus sarmentosus* and *Cocculus trilobus*; this test is usually considered specific for the phenodioxin (diphenylene dioxide) system present in these latter alkaloids (Kondo and Tomita, *J. Pharm. Soc. Japan*, 1932, **52**, 139; Tomita, *ibid.*, p. 147; 1933, **53**, 138). The usual tests for phenolic groups gave negative or indecisive results, but the alkaloid appeared to contain two active hydrogen atoms (Zerewitinoff) and, although it was insoluble in aqueous alkali, it dissolved in Claisen's cryptophenol reagent (*Annalen*, 1919, **418**, 96) and was recovered unchanged on neutralisation. It seemed therefore probable that micranthine contained two phenolic hydroxyl groups. Moreover, from its molecular formula and its occurrence (Pyman, *loc. cit.*) in the same plant source as the bisbenzyl*iso*quinoline alkaloids, daphnandrine and daphnoline (Bick, Ewen and Todd, *loc. cit.*), it was likely that it belonged to the same series, or, more specifically, to the sub-group of the series represented by trilobine and menisarine. These considerations dictated the methods of degradation employed in the present studies.

Heated with methyl iodide in methanolic sodium methoxide, micranthine yielded *OON*-trimethylmicranthine dimethiodide, and this on Hofmann degradation gave the optically-inactive base *OON*-trimethylmicranthinemethine which contained three methoxy-groups. Since the original alkaloid contained only one methoxy-group, it is evident that the others must have been introduced at the initial methylation step, and hence the view expressed above that micranthine contains two phenolic hydroxyl groups is confirmed. A portion of the methine base was treated with methyl iodide and the crystalline dimethiodide submitted to Hofmann degradation, yielding *OO*-dimethylde-*N*-micranthine. Ozonolysis of a second portion of the methine base gave two products, one of which was identified as 5 : 4'-diformyl-2-methoxydiphenyl ether (I; R = Me), previously obtained as a degradation product from a number of bisbenzyl*iso*quinoline alkaloids. The second product, an amino-aldehyde, was converted into its dimethiodide and again degraded by the Hofmann procedure, giving a crystalline substance which, from its analysis and properties, appeared to be a diformyldimethoxydivinylphenodioxin.



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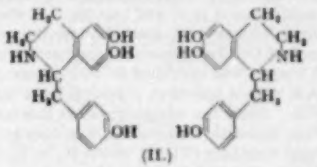

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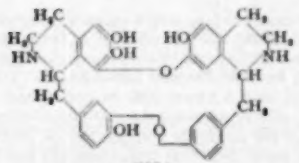
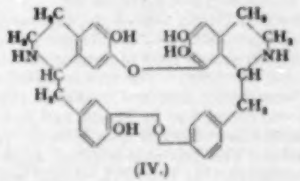


(III.)



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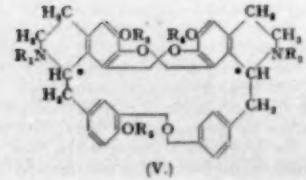

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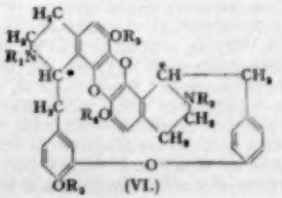


(VI.)

It is clear that a knowledge of the detailed structure of the phenodioxin derivative obtained by the above procedure would go far towards establishing the structure of micranthine. In endeavouring to deduce the structure of these two substances some assistance can be derived from suggestions put forward by Faltis and his co-workers (*Ber.*, 1930, **63**, 806; 1941, **74**, 79; *Annalen*, 1932, **497**, 69; **499**, 301) and by Kondo and Tomita (*Arch. Pharm.*, 1936, **271**, 65) regarding the biogenesis of the biscoclaurine alkaloids. According to their views, these alkaloids are considered to be derived from two molecules of norcoclaurine (II) joined together by a variable number of ether linkages formed as a result of dehydrogenation or dehydration. Thus daphnoline (Bick, Ewen, and Todd, *loc. cit.*) could be derived from the hypothetical bis(norcoclaurine), structures (III) or (IV), by methylation of one imino-group and the two hydroxy-groups at position 6 in each of the *iso*quinoline nuclei; daphnandrine (Bick, Ewen, and Todd, *loc. cit.*) could be formed from daphnoline by methylation of the free hydroxyl group in the benzyl nucleus. Condensation processes of this nature must yield bisbenzyl*iso*quinoline alkaloids which are *O*-substituted at positions 6 and 7 of the *iso*quinoline nuclei, and which may also be substituted at position 8, but only by oxygen in an ether cross-linkage with the other norcoclaurine residue. These conditions hold good for all the biscoclaurine alkaloids so far examined; moreover, no known alkaloid of the group is substituted at position 5 in an *iso*quinoline nucleus. When alkaloids of this group containing a phenodioxin system are considered, only the structural types (V) [which is more conveniently represented as (VI)], (VII), and (VIII) meet the necessary requirements as regards substituents. Of these, only an alkaloid based on (VI) could, by the process of repeated Hofmann degradation, yield a diformyldimethoxydivinylphenodioxin such as was obtained from micranthine. Of the other two structures, (VII) and (VIII), one has been shown to represent trilobine (R = Me) and the other *iso*trilobine (R = Me) (Tomita and Tani, *loc. cit.*) and both yield by the same series of degradations a monomethoxy-phenodioxin derivative. Our conclusion is therefore that micranthine must have a structure of type (VI) and that the aldehyde obtained as final degradation product has structure (IX) (**4 : 9-diformyl-1 : 6-dimethoxy-3 : 8-divinylphenodioxin**). A space model of (VI) shows that there is no undue strain within the molecule only if there is the same stereochemical configuration about each of the asymmetric centres (marked with asterisks). It will be observed that (VI) can readily be derived from (III) or (IV), the hypothetical precursor of daphnoline, which may well be itself the precursor of micranthine in the plant.

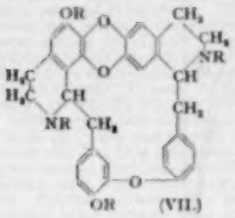
If these arguments and conclusions be accepted, then in micranthine (VI) two of the groups R_2, R_4, and R_5 must be H and one Me. *N*-Methylmicranthine dimethiodide was ethylated and the resulting *N*-methyl-*OO*-diethylmicranthine dimethiodide submitted to Hofmann degradation. The *N*-methyl-*OO*-diethylmicranthinemethine so obtained was ozonised and the neutral product obtained from it was identified as **5 : 4'-diformyl-2-ethoxydiphenyl ether** (I; R = Et) by direct comparison with a specimen prepared by a similar route from repandine (Bick and Todd, *J.*, 1948, 2170). Since the ethoxy-group in this compound must correspond to a hydroxyl group in the starting material, R_3 must be H in micranthine. We are therefore justified in ascribing to micranthine structure (VI), in which R_3 = H, of R_1 and R_5 one is H and the other Me, and of R_2 and R_4 one is H and the other Me.

A structure closely related to (VI) was originally considered, among a number of others, for the alkaloid menisarine by Kondo and Tomita (*loc. cit.*, 1936) but was rejected in favour of two alternative structures more in keeping with the then current formulæ of trilobine and *iso*trilobine (Faltis, *loc. cit.*, 1932). The now accepted structures for trilobine and *iso*trilobine, (VII) and (VIII), were finally proposed by Faltis, Holzinger, Ita, and Schwarz (*loc. cit.*, 1941) and their validity was established by Tomita and Tani (*loc. cit.*), who synthesised the methoxydimethyldiethylphenodioxin obtained from them by reduction of the aldehyde end product of Hofmann degradation. The Japanese workers suggested at the same time that structures (X) and (XI), which correspond to type (V), should again be considered for menisarine. If Kondo and Tomita's earlier experimental evidence (*J. Pharm. Soc. Japan*, 1935, **55**, 100) is re-interpreted in terms of (X) or (XI) for this alkaloid, then it is evident that dihydromenisarine must be represented by (VI; R_1 = H and R_2 = Me or *vice versa*; R_3 = R_4 = R_5 = Me) and *N*-methyldihydromenisarinemethine by (XII). If the formulæ proposed for micranthine (VI; R_1 = H and R_2 = Me or *vice versa*; R_3 = H and R_4 = Me or *vice versa*; R_5 = H) and menisarine (X) or (XI) are correct, then (XII) should also represent *OON*-trimethylmicranthinemethine. The melting points of the two methine bases, together with those of certain of their derivatives and degradation products are compared in Table I, the values for the menisarine derivatives being those given by Kondo and Tomita (*loc. cit.*, 1935); the comparison supports our view that *OON*-trimethylmicranthinemethine and *N*-methyldihydromenisarinemethine are identical.

TABLE I.

	M. p.
N-Methyldihydromenisarinemethine	112°
OON-Trimethylmicranthinemethine	116
N-Methyldihydromenisarinemethine dimethiodide	265 (decomp.)
OON-Trimethylmicranthinemethine dimethiodide	255—260 (decomp.)
De-*N*-dihydromenisarine	208
OO-Dimethylde-*N*-micranthine	210
Aminoaldehyde dimethiodide from menisarine	234 (decomp.)
Aminoaldehyde dimethiodide from micranthine	225—230 (decomp.)
Diformyldimethoxydivinylphenodioxin from menisarine	>300
Diformyldimethoxydivinylphenodioxin from micranthine	no m. p. below 300° >300° gradually decomposes

The dimethiodides (XIII), from which these methine bases (XII) were obtained by Hofmann degradation, each have two asymmetric centres and *a priori* might be identical, enantiomorphic,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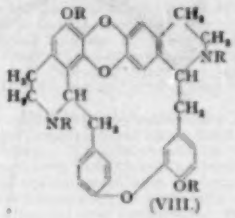
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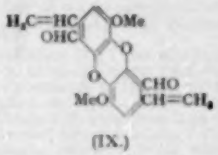
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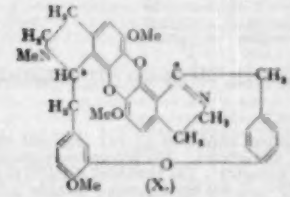
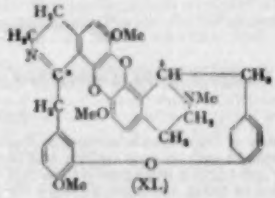

(X.)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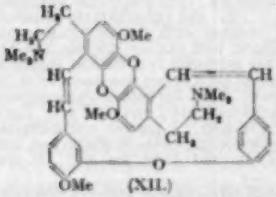
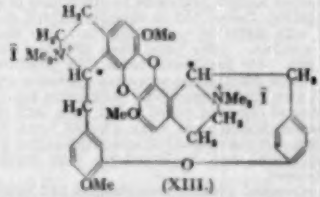
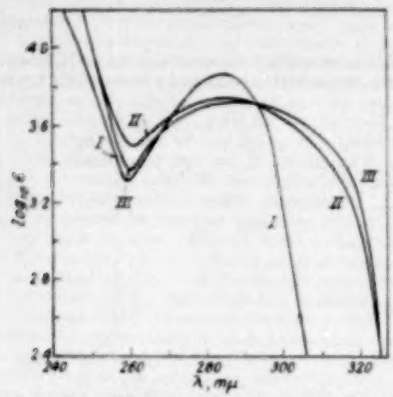

(XII.)


(XIII.)

or diastereoisomeric. As has been mentioned above, however, space models indicate that a molecule such as (XIII), containing asymmetric centres with dissimilar configuration, if it existed at all, would be under great internal strain; the possibility that the two compounds are diastereoisomers can therefore be virtually excluded. To distinguish between the other possibilities, *N*-methyldihydromenisarine dimethiodide was prepared as described by Kondo and Tomita (*loc. cit.*, 1935) from a small sample of menisarine generously provided by Prof. Kondo; it had m. p. 265° (decomp.) and $[\alpha]_D^{20}$ +150° (*c*, 0·1 in water). *OON*-Trimethylmicranthine dimethiodide had m. p. 255—260° (decomp.) and $[\alpha]_D^{20}$ −158° (*c*, 0·4 in water). The quantity of *N*-methyldihydromenisarine dimethiodide was too small to permit of further comparisons, but we feel justified in concluding that it is the enantiomorph of *OON*-trimethylmicranthine dimethiodide. In connection with the formulation of menisarine as (X) or (XI), it is of interest to note that its reduction to dihydromenisarine involves an asymmetric synthesis at carbon atom *a*, the new asymmetric centre formed at this point having the same configuration

as that at carbon atom *b*. This is in accord with the recorded specific rotations of menisarine (+149·4°) and dihydromenisarine (+265·8°); the latter value may be compared with the value −231° found for micranthine.

The absorption spectrum of micranthine is shown in the figure, together with those of trilobine and oxyacanthine. The close similarity between the micranthine ($\lambda_{max.}$ 2860; $\lambda_{min.}$ 2610 A.) and trilobine ($\lambda_{max.}$ 2880; $\lambda_{min.}$ 2610 A.) spectra is presumably due to the common phenodioxin system. A corresponding similarity between the spectra of trilobine, *iso*trilobine, and dihydromenisarine ($\lambda_{max.}$ 2860; $\lambda_{min.}$ 2630 A.) has already been noted by Kondo and Tomita (*loc. cit.*, 1935).



Absorption spectra of oxyacanthine (I), micranthine (II), and trilobine (III) in methanol.

Experimental.

Extraction of Daphnandra micrantha *Bark.*—Finely ground bark (100 g.) was extracted by being stirred overnight with aqueous tartaric acid (500 c.c.; 1%) and filtered. The process was repeated until the extract gave only a weak positive reaction with Meyer's reagent. The combined extracts (4 l.) were concentrated *in vacuo*, and after filtration the solution (500 c.c.) was made strongly alkaline (pH >11) with aqueous sodium hydroxide to precipitate non-phenolic alkaloids. The precipitate was removed by centrifugation, redissolved in aqueous tartaric acid (500 c.c.; 1%), and reprecipitated as before, then washed with water by centrifugation. The washing was repeated until the centrifugate was only slightly alkaline. After being dried, first in a vacuum desiccator over calcium chloride, and finally at 50°/0·1 mm. over phosphoric oxide, this precipitate (5 g.) was extracted in a Soxhlet apparatus with ether. Crude micranthine separated gradually from the ethereal extract and was removed at intervals as a yellowish amorphous solid. Extraction was complete after 5 days; the extract was evaporated and the residue so obtained added to the main bulk of crude micranthine (total yield, 2·3 g.). The residue from the extraction gave weak alkaloid tests with Meyer's reagent; a portion was extracted with chloroform, but the residue left after evaporation of the chloroform extract gave no Millon test, indicating that daphnoline and daphnandrine were absent (Bick, Ewen, and Todd, *loc. cit.*); it could not be crystallised.

The combined alkaline centrifugates and washings obtained after the non-phenolic alkaloids in the original extract had been precipitated were saturated with carbon dioxide and the precipitate separated by centrifugation. After being washed and dried as described above, the precipitate (0·7 g.) was exhaustively extracted with ether in a Soxhlet apparatus. After removal of the ether, the residue (0·2 g.), which could not be crystallised, gave a weakly positive Meyer reaction but the Millon test and the diphenylene dioxide (phenodioxin) test (Kondo and Tomita, *loc. cit.*, 1932) were negative.

The yield of crude micranthine from a large-scale extraction of bark (2·2 kg.) by the same procedure was 45 g.

Micranthine.—A sample of crude micranthine (5·0 g.) was dissolved in dry benzene (500 c.c.) and poured on a column of neutral alumina (*ca.* 150 g.). The column was washed with chloroform, the washings evaporated to dryness *in vacuo*, and the residue (4·4 g.) moistened with methanol, whereupon it set to a mass of colourless needles. Recrystallised from ethyl acetate and then from methanol, and finally dried at 100°/0·1 mm., micranthine formed colourless needles which on being heated softened at 185° and melted at 194—196° (Pyman, *loc. cit.*, records sintering from about 190° and gradual melting and decomposition at 196°). Admixture with a sample of micranthine isolated by Pyman did not depress the m. p. Micranthine is sparingly soluble in methanol, ethyl acetate and benzene, rather more soluble in chloroform and ethanol, and very slightly soluble in ether. In chloroform it had $[\alpha]_D^{20}$ −231° (*c*, 0·7). With Fröhde's reagent it gave an indigo solution, becoming emerald green. With concentrated sulphuric

acid containing a trace of nitric acid, micranthine gave a deep-blue colour, identical with that produced by trilobine and menisarine in parallel tests. No coloration was produced with ferric chloride or with Millon's reagent in the cold, but when warmed with Millon's reagent micranthine gave a faint pink colour. Micranthine was insoluble in aqueous alkali, but dissolved in Claisen's cryptophenol reagent (*loc. cit.*). On carbon dioxide being passed through this solution a white precipitate was formed which was removed by centrifugation; recrystallisation yielded micranthine, m. p. and mixed m. p. 194—196° (Found: C, 72·1; H, 5·0; N, 4·9; MeO, 6·4; MeN, 3·9, 5·2; active H, 0·42. Calc. for $C_{34}H_{32}O_4N_2$: C, 72·3; H, 5·7; N, 5·0; MeO, 5·5; MeN, 5·2; active H, 0·35%).

Micranthine Sulphate.—A solution of micranthine (1·0 g.) in hot aqueous sulphuric acid (100 c.c.; 0·5%) gave a micro-crystalline precipitate of micranthine sulphate (1·0 g.) on cooling. Recrystallised from hot water, micranthine sulphate formed colourless needles, m. p. 305—310° (decomp.), $[\alpha]_D^{20}$ −127° (*c*, 0·5 for anhydrous salt in water) (Found: C, 57·7; H, 5·4; N, 4·2; loss at 110°/0·1 mm., 6·6. Calc. for $C_{34}H_{32}O_4N_2,H_2SO_4,2\frac{1}{2}H_2O$: C, 57·3; H, 5·2; N, 4·0; H_2O, 6·4%).

OON-*Trimethylmicranthine Dimethiodide.*—Micranthine (5·0 g.) was suspended in dry methanol (300 c.c.) and methyl iodide (10 c.c.) was added, followed by methanolic sodium methoxide (0·5 g. of sodium dissolved in 15 c.c. of methanol). The mixture was heated under reflux for 6 hours, a similar amount of sodium methoxide was added, and heating continued for a further 6 hour period; the process was repeated until in all 5 such additions had been made. The solvent was removed *in vacuo*, and the residue taken up in hot water. The yellow amorphous solid which was deposited on cooling the aqueous solution was collected and redissolved in boiling water, and the solution boiled with a little copper powder during 10 minutes. The filtered solution on being set aside deposited a cream-coloured precipitate which was filtered off and dissolved in hot methanol. From the solution colourless needles (4·9 g.) of the *dimethiodide* separated; m. p. 255—260° (decomp.), $[\alpha]_D^{20}$ −158° (*c*, 0·4 for anhydrous salt in water) (Found: C, 48·4; H, 5·6; N, 2·9; loss at 110°/0·1 mm., 8·9. $C_{36}H_{44}O_4N_2I_2,4\frac{1}{2}H_2O$ requires C, 48·2; H, 5·5; N, 2·9; H_2O, 8·3%).

OON-*Trimethylmicranthinemethine.*—*OON*-Trimethylmicranthine dimethiodide (3 g.) was dissolved in water (1 l.) and shaken with freshly prepared silver oxide (from 3·0 g. of silver nitrate) until the solution was free from iodide ions (2 hours). The filtered solution was concentrated to 100 c.c. under reduced pressure and heated on the steam-bath with aqueous potassium hydroxide (25 c.c.; 50%). The yellowish resin, which slowly separated, was extracted from the cooled solution with ether from time to time. Heating and extraction were continued until no more resin was formed (about 2 hours). The combined ether extracts were dried (Na_2SO_4) and evaporated; the resinous residue (1·5 g.), when moistened with methanol, crystallised in colourless needles. Recrystallised from methanol it had m. p. 115°, $[\alpha]_D^{20}$ 0·0° (*c*, 0·8 in chloroform). It gave no coloration with ferric chloride, was Millon negative, and was insoluble in Claisen's cryptophenol reagent (Found: C, 73·7; H, 6·6; N, 4·5; MeO, 12·7. Calc. for $C_{36}H_{42}O_4N_2$: C, 73·6; H, 6·7; N, 4·4; MeO, 14·7%).

OON-*Trimethylmicranthinemethine Dimethiodide.*—*OON*-Trimethylmicranthinemethine (0·5 g.) was dissolved in warm methanol (50 c.c.) and boiled under reflux during 15 minutes with methyl iodide (0·5 c.c.). The solution was evaporated to about half its original volume and set aside. Colourless needles (0·5 g.) of *OON*-trimethylmicranthinemethine dimethiodide separated, and after recrystallisation from methanol had m. p. 255—260° (decomp.) (Found: C, 50·4; H, 5·0; N, 3·4; loss at 110°/0·1 mm., 6·3. Calc. for $C_{41}H_{44}O_4N_2I_2,3\frac{1}{2}H_2O$: C, 50·2; H, 5·6; N, 2·9; H_2O, 6·4%).

OO-*Dimethyl*-N-*micranthine.*—*OON*-Trimethylmicranthinemethine dimethiodide (0·2 g.) was dissolved in water (50 c.c.) and heated on the steam-bath with sodium hydroxide solution (5 c.c.; 30%). Trimethylamine was evolved, and a resin slowly separated. The latter was extracted from the cooled solution with chloroform, and the heating and extraction repeated until no more resin separated (30 minutes). The chloroform solutions were combined, washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue, moistened with ethanol, crystallised in colourless needles; recrystallised from ethanol, it had m. p. 210° (Found: C, 75·3; H, 5·8. Calc. for $C_{33}H_{32}O_4,C_2H_6O$: C, 75·2; H, 5·8%).

Ozonolysis of OON-*Trimethylmicranthinemethine.*—*OON*-Trimethylmicranthinemethine (5 g.) was dissolved in aqueous acetic acid (200 c.c.; 1%), the solution cooled in ice, and a stream of ozone (5%) passed through it. The sticky yellowish mass which slowly separated was extracted from time to time with ether. Ozonolysis was continued until no further cloudiness appeared in the liquid and a test portion of the solution gave no precipitate with ammonia solution (1½ hours). The ether extracts were washed with sodium carbonate solution until free from acid, dried (Na_2SO_4), and evaporated. The residue (1·1 g.) was recrystallised from light petroleum and had m. p. 77—78° undepressed in admixture with a sample of 5:4′-diformyl-2-methoxydiphenyl ether prepared from repandine (Bick and Todd, *loc. cit.*) (Found: C, 70·3; H, 5·2. Calc. for $C_{15}H_{12}O_4$: C, 70·3; H, 4·7%).

The aqueous solution from the ozonolysis was freed from peroxides by shaking it with palladised charcoal, and from amine oxides by shaking it with hydrogen for 15 minutes. The solution was now filtered, made strongly alkaline with sodium hydroxide, and thoroughly extracted with chloroform. The combined extracts were dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The residue (1·1 g.) was dissolved in methanol (20 c.c.) and heated under reflux with methyl iodide (2 c.c.) for 30 minutes. The solvent was now removed and the residue dissolved in hot methanol and set aside. The amorphous amino-aldehyde dimethiodide which separated was further purified by the same process and was finally obtained as yellowish micro-prisms, m. p. 225—230° (decomp.) (Found: C, 43·2; H, 5·2; N, 4·4. Calc. for $C_{33}H_{34}O_4N_2I_2$: C, 43·0; H, 5·0; N, 3·9%).

4:9-*Diformyl*-1:6-*dimethoxy*-3:8-*divinylphenodioxin* (IX).—The above amino-aldehyde dimethiodide (0·5 g.) was dissolved in water (100 c.c.), and the solution made alkaline with potassium hydroxide solution (5 c.c.; 50%) and heated on the steam-bath. Trimethylamine was evolved and the yellowish precipitate which formed was extracted from time to time with chloroform. Heating was continued until no further precipitate appeared and the combined extracts were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue so obtained (0·2 g.) was dissolved in benzene (20 c.c.) and chromatographed on a column of neutral alumina (about 10 g.). Elution with

chloroform gave a fraction which on evaporation yielded a yellowish crystalline powder (50 mg.). Recrystallised from chloroform, the product on being heated gradually decomposed above 300° without melting. It gave a positive Schiff's test and a blue colour with concentrated sulphuric acid containing a trace of nitric acid, indicating the presence of a diphenylene dioxide (phenodioxin) system. A solution in glacial acetic acid gave a blue colour on addition of concentrated sulphuric acid, indicating the presence of an *O*-vinylaldehyde grouping. On catalytic hydrogenation, the substance took up 2 mols. of hydrogen rapidly and a further 2 mols. more slowly (Found: C, 68·4; H, 4·9; MeO, 16·9. Calc. for $C_{20}H_{14}O_4$: C, 68·2; H, 4·6; MeO, 17·6%).

N-Methyl-OO-diethylmicranthine Dimethiodide.—Micranthine (1 g.) was dissolved in boiling methanol (100 c.c.) and heated under reflux with methyl iodide (2·5 c.c.) for 6 hours. The solvent was removed *in vacuo*, and the yellowish resinous residue dissolved in boiling ethanol (250 c.c.). The solution was boiled under reflux with ethyl iodide (3 c.c.) and ethanolic sodium ethoxide (0·08 g. of sodium in 5 c.c. of ethanol). A further four additions of similar quantities of sodium ethoxide were made at intervals of 6 hours to the boiling solution, then the solvent was removed *in vacuo*, and the residue dissolved in boiling water. The yellowish resin which separated on cooling was redissolved in hot water, and the solution boiled with a a little copper powder for 10 minutes then filtered and allowed to cool. The amorphous product which separated was redissolved in hot methanol, and the solution on being kept deposited colourless needles (0·8 g.), m. p. 250—255° (decomp.) (Found: C, 49·8; H, 5·5; N, 2·9; loss at 110°/0·1 mm., 7·8. $C_{41}H_{44}O_6N_2I_2,4H_2O$ requires C, 49·7; H, 5·7; N, 2·8; H_2O, 7·3%).

N-Methyl-OO-diethylmicranthinemethine.—An aqueous solution of *N*-methyl-*OO*-diethylmicranthine dimethiodide (1 g. in 100 c.c.) was heated on the steam-bath with aqueous potassium hydroxide (5 c.c.; 50%). The yellowish resin which separated was removed from time to time and heating was continued until no further resin was formed. The solution was cooled and thoroughly extracted with ether, and the extracts were combined with an ethereal solution of the resin. After the ether solution had been washed with water and dried (Na_2SO_4), the ether was removed and the residue moistened with methanol. The product crystallised in colourless needles (0·6 g.) which, after recrystallisation from methanol, had m. p. 121°. A mixed-m. p. with *OON*-trimethylmicranthine gave a depression of about 20° (Found: C, 75·9; H, 7·0; N, 4·8. $C_{41}H_{46}O_4N_2$ requires C, 76·3; H, 6·9; N, 4·2%).

Ozonolysis of N-Methyl-OO-diethylmicranthinemethine.—*N*-Methyl-*OO*-diethylmicranthinemethine (0·5 g.) was ozonised in dilute acetic acid solution as described above for *OON*-trimethylmicranthinemethine. The resin which separated was extracted with ether and the extract washed first with aqueous sodium carbonate and then with water, dried (Na_2SO_4), and evaporated. The residue, recrystallised from light petroleum, formed colourless needles (0·1 g.), m. p. 60°, identical (mixed m. p.) with 5:4′-diformyl-2-ethoxydiphenyl ether obtained by an analogous procedure from repandine (Bick and Todd, *loc. cit.*) (Found: C, 71·5; H, 5·4. Calc. for $C_{14}H_{14}O_4$: C, 71·1; H, 5·2%).

N-Methyldihydromenisarine Dimethiodide.—Menisarine (8 mg.) was dissolved in acetic acid (2 c.c.; 10%) and the yellowish solution heated on the steam-bath with powdered zinc (20 mg.) with occasional stirring, until colourless. The residue left on filtration was washed with small quantities of hot water, and the combined filtrate and washings were made alkaline with ammonia solution and thoroughly extracted with chloroform. The chloroform solution was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue (7 mg.) was dissolved in methanol (1 c.c.) and heated under reflux with methyl iodide (0·01 c.c.) for 30 minutes. After removal of the solvent under reduced pressure, the residue was dissolved in water (2 c.c.) and boiled with a small amount of charcoal. The solution was filtered, the residue washed with hot water, and the combined filtrate and washings evaporated to a small bulk under reduced pressure and set aside. *N*-Methyldihydromenisarine dimethiodide (4·70 mg.; dried at 110°/0·1 mm.), $[\alpha]_D^{20}$ +150° (*c*, 0·1 in water) separated from solution; it could not be obtained crystalline.

Absorption Spectra of Micranthine, Trilobine, and Oxyacanthine.—The absorption spectra of the above alkaloids was determined in methanol solution (about 10^{-4}/10,000) by using a Beckman quartz spectrophotometer. The curves are shown in the figure. The values obtained for wave-length and, in parentheses, extinction coefficients at the minima and maxima, respectively, were: micranthine, 2610 (3020), 2860 (5310); trilobine, 2610 (2240), 2880 (3250); and oxyacanthine 2600 (2040), 2850 A. (7090).

We express our gratitude to Mr. C. J. Trist of the Queensland Forestry Department and Mr. L. J. Webb of the Commonwealth Scientific and Industrial Research Organisation, Australia, for supplies of bark used in this investigation, to Prof. H. Kondo for gifts of menisarine and trilobine, and to the British Council and the Australian National University for scholarships held by one of us (I. R. C. B.).

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334. *Branched-chain Super-esters.*

By G. W. Youngson and H. W. Melville.

Branched-chain super-ester molecules have been synthesised by the following method. Linear polyethylene adipate polymers were prepared by conventional methods using an excess of ethylene glycol to produce terminal hydroxyl groups. This was confirmed by estimating chemically the number of end-groups and measuring osmotically the number of polymer molecules present in a given sample. These linear polymers were then degraded to a small extent and allowed to react with pentaerythritol, dipentaerythritol, and trishydroxymethylpropane in limited amounts. By end-group determinations and osmotic-pressure experiments it was shown that branched-chain molecules had been produced. The viscometric behaviour of solutions of these molecules was determined.

Part I.

Most of the investigations into the synthesis and structure of high polymers have been concerned with linear molecules or with three-dimensional networks. Very little work has been attempted with branched-chain molecules. Such molecules are of interest for many reasons. In the early stages of the production of three-dimensional molecules they must have a transitory existence. Similarly, in the later stages of vinyl polymerisations the process of transfer to the polymer will give rise to branched molecules provided that termination of polymerisation only involves disproportionation between polymer radicals. There is therefore the problem of devising synthetic methods in both systems to isolate such structures, if possible unmixed with linear or three-dimensional molecules. Interest also attaches to the thermodynamics and the hydrodynamical behaviour of solutions of branched-chain molecules, for there is relatively little guidance from theory as to the behaviour to be expected. Conversely, such knowledge may yield some information about the extent of branching in polymers whose structure cannot easily be determined, for example, when end-group analysis is impracticable.

This paper is concerned with the problem of synthesis. The ideal way in which to synthesise a branched-chain polymer is to start with a linear polymer to which suitable reactive groups are attached. Another series of linear molecules containing only one terminal reactive group capable of reacting with the backbone is prepared and the two are brought together under suitable conditions. This approach was attempted in the following way but was unsuccessful. The backbone was polyvinyl alcohol of known molecular weight. A monofunctional polymer was made by polymerising styrene in presence of carbon tetrachloride so that each polystyrene molecule possessed a CCl_3 end-group. Unfortunately, it proved impossible to convert any appreciable fraction of CCl_3 groups into CO_2H. This method was therefore abandoned.

The other scheme of rather less flexibility consisted in using a super-ester with suitable terminal groups and condensing such a molecule with a polyhydric alcohol or polybasic acid. After some trials the system finally used was that of polyethylene adipate with terminal hydroxyl groups, with the polyhydric alcohols, pentaerythritol, dipentaerythritol, and trishydroxymethylpropane (2 : 2-bishydroxymethylbutan-1-ol). The problem in such systems is to achieve incorporation of the polyhydric alcohol without the formation of any appreciable amount of insoluble three-dimensional polymer. The advantage of this kind of system is that at the end of each branch in the molecule there is a hydroxyl group whose concentration can be determined by standard methods.

Experimental.

Preparation of the Parent Polymer.—On account of (*a*) the availability of monomers in a relatively pure state and (*b*) the viscosity of the resultant polymer, polyethylene adipate (obtained by the intercondensation of adipic acid and ethylene glycol) was selected as the most suitable polymer from which synthesis of branched-chain polymers could be initiated. As absolute purity of the final product was essential, both reactants were purified before interaction, the adipic acid by recrystallisation (with use of charcoal) from ethyl alcohol, and the ethylene glycol by refluxing over lead monoxide followed by distillation of the fraction of b. p. 196—197°. No catalyst was used in the reaction, as the introduction of toluene-*p*-sulphonic acid, the usual catalyst employed, might have led to errors in physical measurements subsequently made on the linear and branched polymers.

The method of polyesterification chosen was that originally devised by Carothers, in which ester interchange was employed to produce high molecular weight polyesters from a reaction mixture in which the glycol was in stoicheiometric excess of the dibasic acid used (Carothers and Dorough, *J. Amer. Chem. Soc.*, 1930, **52**, 711; Carothers, *Chem. Reviews*, 1931, **8**, 353). Essentially, the method consists in refluxing a mixture containing a 3 : 1 molar mixture of ethylene glycol and adipic acid for 24 hours in a stream of oxygen-free gas, preferably nitrogen at atmospheric pressure. The mixture then consists of a solution of the diglycol ester of adipic acid [di-(2-hydroxyethyl) adipate] in ethylene glycol :

$$2HO\text{-}[CH_2]_2\text{-}OH + HO_2C\text{-}[CH_2]_4\text{-}CO_2H \longrightarrow HO\text{-}[CH_2]_2\text{-}O\text{-}CO\text{-}[CH_2]_4\text{-}CO\text{-}O[CH_2]_2\text{-}OH$$

In the second part of the process, the nitrogen stream is passed through drying towers of sulphuric acid and calcium chloride to ensure the greatest degree of condensation and to obviate any hydrolytic degradation of the polyester formed. The pressure of the dry oxygen-free nitrogen is then reduced to 0·1—0·25 mm. of mercury by means of a Speedivac pump regulated by a gas leak, and under the influence of heat and agitation excess of ethylene glycol is removed from the solution, followed by a further quantity of ethylene glycol eliminated as a by-product as the condensation reaction proceeds:

$$n\text{HO}\cdot[\text{CH}_2]_2\cdot\text{O}\cdot\text{CO}\cdot[\text{CH}_2]_4\cdot\text{CO}\cdot\text{O}\cdot[\text{CH}_2]_2\cdot\text{OH}$$

$$\downarrow$$

$$\text{HO}\cdot([\text{CH}_2]_2\cdot\text{O}\cdot\text{CO}\cdot[\text{CH}_2]_4\cdot\text{CO}\cdot\text{O})_n\cdot[\text{CH}_2]_2\cdot\text{OH} + (n-1)(\text{CH}_2\cdot\text{OH})_2$$

Polyethylene adipate.

From the method of preparation, it is evident that a large proportion of the polyester molecules so formed will possess two terminal hydroxyl groups per molecule.

Condensation is continued usually for 8—12 hours, after which ethylene glycol vapour ceases to be removed and condensation is complete under the conditions of experiment. The molecular weights obtained by this procedure range from 8000 to 10,000 approximately, and the polymers possess the property of "cold-drawing," which may be adopted as a simple test of the extent of condensation.

Molecular-weight Determination.—(a) *Chemical method* [Private communication from Imperial Chemical Industries Limited (Dyestuffs Division)]. Molecular weights of polyesters prepared by the method outlined above can be determined by measurement of the number of alcoholic and acidic end-groups present in a given weight of polyester, and, from the knowledge that such polymers can, from the mechanism of condensation, possess two end-groups only, the molecular weight may be calculated.

The alcoholic end-groups are determined by the standard acetylation procedure and are expressed as the "acetyl value" of the polymer (mg. of potassium hydroxide per g. of polymer).

The acidic end-groups are determined by titrating approximately 8 g. of the polyester in neutral alcohol with standard caustic alkali and are expressed as the "acid value" of the polymer (mg. of potassium hydroxide per g. of polymer).

If S is the sum of the acetyl and acid values obtained for the polymer, the amount of hydroxyl group per g. of polymer is given by $17S/56$ and, since polyester molecules contain two end groups only, the weight of polymer containing the equivalent of two hydroxyl groups gives a measure of the molecular weight of the polymer.

Chemical methods of molecular-weight determination are, of necessity, number average values, *i.e.*, $\Sigma M_x N_x/\Sigma N_x$, where M_x is the molecular weight of an x-mer and N_x is the total number of x-mers. Any variations which introduce structural changes or an increase in the number of hydroxyl groups will alter the apparent molecular weight obtained.

(b) *Osmotic method.* The instrument used to measure osmotic pressures was closely similar to that described by Fuoss and Mead (*J. Physical Chem.*, 1943, **47**, 59). The cells, instead of being fashioned from two stainless-steel plates, were cut from Δ-bronze forgings with valves of stainless steel, and the screw joints in the side-arms and capillary tubes had lead-foil washers. To lessen the volume of solution and therefore external temperature effects, the capillary tubes of 1-mm. diameter were sealed directly to the metal in the glass-to-metal seals.

Temperature was maintained constant within less than ±0·01° by immersion in a thermostat controlled by a toluene–mercury regulator and "Thyratron" relay. In place of the partly denitrated nitrocellulose films used by Fuoss and Mead (*loc. cit.*) as the semi-permeable membrane of the osmometer, a disc of bacterial cellulose (Masson, Menzies, Cruickshank, and Melville, *Nature*, 1946, **157**, 74) was used in measurements by the dynamic method, while non-moisture-proof Cellophane was used for a static method to obtain molecular weights lower than those obtainable by the dynamic method.

When using the dynamic method, it was found that in dealing with polyester solutions, membranes re-swelled in alcohol–water mixtures containing 0—40% alcohol were of little use even with a membrane of 4-mm. wet thickness, for with all such membranes a considerable drift was apparent in the graphs of osmotic pressure against time. To obviate this, the thickest membranes (5—6 mm. in the swollen state) were used and by re-swelling these in 60 : 40 alcohol–water a membrane with a lower molecular weight limit of 25,000 could be obtained, while a membrane re-swelled in 70 : 30 alcohol–water gave a corresponding limit of 20,000. Mixtures of higher alcohol content could be used to obtain membranes with an even lower limit, but the time intervals required to obtain a good osmotic pressure–time curve became excessive and equally good results could be obtained statically with little increase in the time of experiment.

In the actual experiments, dilute solutions containing 0·5—1·0 g. of polymer per 100 g. of solution were used initially and a pair of matched curves was obtained, from which the osmotic pressure (π) appropriate to that concentration (c) was obtained. The solution was then diluted repeatedly, an osmotic pressure corresponding to each dilution being obtained (Masson, unpublished). A graph of π/c against c was extrapolated to zero concentration to give a value for $[\pi/c]_0$ which was then substituted in the equation

$$[\pi/c]_0 = 10{,}330 \times 0{\cdot}0821T/M$$

where 10,330 is the conversion factor from l.-atm. per °c. 100 c.c. to cm. of water per °c., T is the absolute temperature, and M the molecular weight of the solute. π/c was measured in g. of solute per 100 g. of solution, and the above constants apply irrespective of the solvent used.

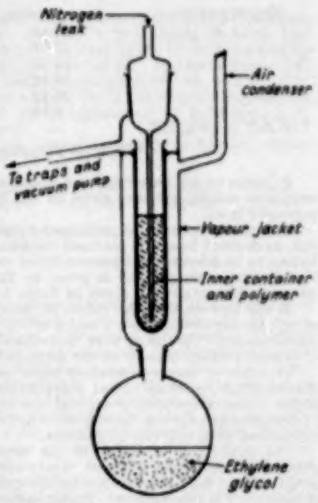
For measurements on polymers of molecular weight <20,000, a "static" membrane was prepared from non-moisture-proof Cellophane, according to the method used by Carter and Record (*J.*, 1939, 660). The membrane of approximately 0·04-cm. dry thickness was prepared in the following stages: (a) Immersion for 1 hour in 60 : 40 ethanol–water to remove glycerol present as plasticiser.

(*b*) Immersion for a further 4 hours in a bath of the same composition with 1% of ammonia added to remove fatty acids. (*c*) Immersion overnight in a bath of 60 : 40 ethanol–water, by which the permeability of the membrane was determined. Alteration of the composition of this bath alters the permeability accordingly. (*d*) Displacement of the absorbed water by alcohol, followed by displacement of the alcohol by the solvent to be used experimentally, in this case chloroform, the bath being changed repeatedly until all the alcohol had been removed.

In the manner described above for the dynamic method, a π/c–c curve can again be drawn to find $[\pi/c]_0$, the limiting value of π/c at zero concentration.

As this method of obtaining osmotic pressures and molecular weights entails protracted experimental work, one reading for π/c was taken at a concentration giving an osmotic pressure of approximately 1 cm. of polymer solution. At lower molecular weights, the difference between the value of the molecular weight given by this reading and that given by the actual value of $[\pi/c]_0$ is very small and is within experimental error. In this way, the time of experiment can be greatly reduced.

FIG. 1.



The Synthesis of Branched-chain Polymers.—It is well known that, when an organic compound which possesses more than two functional groups is co-condensed in appreciable proportions with monomers which by themselves are capable of linear-molecule formation only, the resulting product is a gel which is totally, or largely, insoluble in all solvents. As this is the direct result of condensation in three dimensions, as opposed to two dimensions in the case of a linear polycondensed molecule, it was thought that under chosen conditions an intermediate stage in the condensation should occur at which branched molecules were present. Branching must, of course, be a necessary preliminary to cross-linking, but under normal conditions the gelation reaction takes place so suddenly that little progress has been made in determining the structure of intermediate products.

In order to carry out an investigation on the alteration of the physical properties occasioned by the introduction of a polyfunctional reactant into the condensation process, a series of condensations was carried out in the apparatus shown in Fig. 1, in which successively greater percentages of pentaerythritol, $C(CH_2{\cdot}OH)_4$, were added to a sample of polyethylene adipate which had been polymerised to its fullest extent under the conditions of experiment. After addition of the pentaerythritol the reaction mixture was heated by means of a vapour-bath of ethylene glycol for two hours, during which the polyester depolymerised slightly, allowing the pentaerythritol to dissolve and react with the polymer. Condensation was then carried out as before, exhaustively for at least eight hours, during which a quantity of the original pentaerythritol volatilised out of the melt. A series of five polymers was prepared in this way, containing initially 1·0, 1·5, 1·8, 1·9, and 2·0% of pentaerythritol, the last being a gel.

It was evident, therefore, that under the conditions of the experiment a critical percentage of pentaerythritol could be added below which gelation would not take place. The copolymers so formed were soluble in the usual solvents with slightly greater difficulty than was linear polyethylene adipate, probably owing to an increase in viscosity.

Molecular-weight determinations were carried out on all these polymers, except that containing 1% of pentaerythritol, by means of dynamic osmometry giving π/c–c curves. The copolymer containing 1% of pentaerythritol gave "drifting" in the dynamic osmometer, and the value was therefore obtained statically. The results are given in the following table.

Polymer.	$[\pi/c]_0$.	Mol. wt.
Ethylene adipate + 1·0% of P.E.	14·60	17,000
" " 1·5% of P.E.	10·00	25,000
" " 1·8% of P.E.	6·70	37,000
" " 1·9% of P.E.	5·25	47,500

P.E. = pentaerythritol.

The value given by the copolymer containing 1·9% of pentaerythritol approximates to a four-fold increase in molecular weight compared with polyethylene adipate prepared under identical conditions. The acetyl and acid values of the 1·9% copolymer and of linear polyethylene adipate disclosed a doubling of the number of end groups per molecule, *i.e.*, four in place of two. With smaller quantities of pentaerythritol it is evident that the polymers will consist of linear together with branched-chain molecules.

From these details, it would appear that the pentaerythritol has acted as a nucleus for growth in four directions, each of the arms being of approximately equivalent length. In addition, any attempt to increase the percentage of added pentaerythritol results in gelation. It therefore appears that immediately before gelation the molecules are, on the average, essentially cruciform in shape.

In order to confirm this theory, it was necessary to prepare a series of such copolymers of penta-

erythritol with linear polyethylene adipate, of differing molecular weights. Only in this way can the various physical properties of such polymers be typified and characterised.

When sufficient polyfunctional compound is added in the copolymerisation reaction to result eventually in the production of a gel, it should be possible, if the above theory is correct, to terminate the condensation process immediately before the gel point and to obtain thereby molecules whose average structure is completely branched in four directions. Again, with the addition of progressively larger percentages of polyfunctional compound, the molecular weights of these molecules so formed should be correspondingly reduced since branching will occur earlier in the condensation reaction (see Table I). The depolymerisation and recondensation procedure used was as previously described, the reaction being interrupted immediately before the gel point. This procedure is largely a matter of experience in recognising the signs of the onset of gelation during which the melt passes from a finite to an infinite viscosity.

TABLE I.

Copolymer no.	Acetyl value.	Acid value.	Chemical mol. wt.	Osmotic mol. wt.
1	22·68	0·89	9,500	10,000
2	21·30	0·92	10,000	19,500
3	15·60	0·78	14,000	15,000
4	18·45	0·86	11,500	20,000
5	13·70	0·96	15,500	17,000
6	8·89	0·88	23,000	23,000
7 (E.A.* + 1·9% P.E.)	—	—	—	47,500

* E.A. = Polyethylene adipate; P.E. = pentaerythritol.

A series of six polymers was prepared in this fashion, and to this series was added the highest molecular weight polymer given by the last series of experiments which, in effect, gives seven similar polymers in all.

Osmotic and chemical molecular-weight determinations were again used as a basis of comparison, but, as distinct from the previous chemical molecular weight determinations in which the molecule was known to be dihydric, the present series were evaluated on the basis that each molecule was tetrahydric. The molecular weight (M) is given by $224 \times 1000/S$, where S is the sum of the acid and the acetyl values. The results are given in Table I.

It will be seen that the values for molecular weight given by the two methods show good agreement except for copolymers nos. 2 and 4 which will be discussed later. It appears that there is considerable justification for the theory that, immediately before gelation, all the molecules formed by copolymerisation of pentaerythritol possess on the average four end groups.

In order to discover whether other polyfunctional compounds could be made to undergo similar condensation reactions, linear polyethylene adipate was copolymerised first with dipentaerythritol, a dimer of pentaerythritol possessing six hydroxyl groups per molecule, and secondly with 1 : 1 : 1-trishydroxymethylpropane, having three hydroxyl groups; both these copolymers are capable, under given conditions, of giving rise to gelation.

The method of synthesis in the case of dipentaerythritol was identical with that used in the preparation of pentaerythritol copolymers, except for the precaution of adding a slightly greater percentage of dipentaerythritol to offset its greater volatility at ordinary pressures when raised to the temperature of experiment. Under reduced pressure, this volatility is even more marked.

A series of nine copolymers was prepared of which one showed no signs of gelling. Details of chemical and osmotic molecular weights were again obtained, as shown in the following table, the chemical

Polymer no.	Acetyl value.	Acid value.	Mol. wt. (chemical).	$[\eta/c]_{sp.}$	Mol. wt. (osmotic).
1	11·35	0·26	29,000	8·96	27,000
2	11·98	0·25	24,000	10·93	23,000
3	22·90	0·31	15,000	16·05	15,500
4	24·30	0·49	13,800	18·10	13,700
5	27·10	0·42	12,200	17·65	14,000
6	31·48	0·42	10,500	22·95	10,800
7	36·19	0·42	9,200	26·80	9,300
8	39·94	0·61	8,300	31·40	8,000

molecular weight being calculated on the basis of six hydroxyl groups per molecule. Again, agreement between chemical and osmotic molecular weights is very good and appears to justify the determination of chemical molecular weights on the basis of six hydroxyl groups per molecule. One point is noteworthy: although six hydroxyl groups are present per molecule, there is a definite threshold effect above which gelling occurs, and below which gelling does not take place. In the pentaerythritol series, it appeared that the introduction of a second nucleus was necessary for gelation, brought about by the increase in the number of hydroxyl groups per molecule and consequently in the opportunity for intramolecular condensation. In dipentaerythritol polymers, there are already six hydroxyl groups, but these apparently do not react intramolecularly until a second nucleus is introduced.

Copolymerisation of ethylene adipate with 1 : 1 : 1-trishydroxymethylpropane presented considerable difficulty in view of its great volatility under experimental conditions. Even at ordinary pressures, its vapour pressure was sufficiently high for a notable proportion of the compound originally added to distil out of the reaction mixture. To minimise this effect, modifications in experimental procedure were necessary.

The reaction was carried out initially for two hours at 100°, and then for two hours in a vapour-bath of ethylene glycol (197°), both at atmospheric pressure. This was followed by condensation at the

latter temperature. Even with this method of experimentation, the greater part of the trishydroxymethylpropane was lost by volatilisation.

Eight copolymers were prepared, of which two gelled and another showed no signs of gelling. The remaining five polymers were subjected to the tests discussed above. As, in this case, the number of groups present per molecule was unknown, acid and acetyl values were measured, and molecular weights were determined by the static osmometer. From these quantities, the number of hydroxyl groups was calculated for each polymer molecule, as follows. It will be seen that the number of hydroxyl groups per

Polymer no.	Acetyl value.	Acid value.	$[\eta/c]_{sp.}$	Mol. wt. (osmotic).	No. of OH groups.
1	9·30	0·28	13·13	19,000	3·25
2	14·35	0·37	16·65	14,900	3·92
3	16·60	0·30	16·90	14,700	4·44
4	21·80	0·33	23·49	10,500	4·17
5	42·30	0·35	33·62	7,400	5·63

molecule varies considerably but is, on the average, close to four. Divergences in the cases of polymers nos. 1 and 5 may be ascribed to the experimental difficulties. For No. 1, it is highly probable that insufficient of the trifunctional compound was present to cause gelation, but owing to the considerably higher viscosities encountered it was difficult to decide whether the melt would gel. The discrepancy with No. 5 can be explained by the comparatively large amount of trishydroxymethylpropane added. Any unchanged functional compound would result in increased acetyl values, but in the osmotic experiments such small molecules can pass through the membrane and set up an equilibrium on both sides of it, while the polymer molecules exert their normal osmotic pressure.

Calculated on the basis of four hydroxyl groups per molecule, the comparison is as follows: Again

Polymer no.	1	2	3	4	5
Chemical mol. wt.	23,000	15,200	13,300	10,200	8,300
Osmotic mol. wt.	19,000	14,900	14,700	10,500	7,400

agreement appears to be close, two molecules of trishydroxymethylpropane being required to satisfy the experimental results.

Part II.

Branched-chain Polymers.—In view of the necessity for a greater understanding of the effects of shape and size of polymer molecules on their physical characteristics, particularly viscosity, all three series of copolymers were subjected to viscometry in chloroform solution by means of an Ostwald viscometer. In order to effect a strict comparison, the measurement taken was the limiting viscosity of the polymer, which is given by the expressions $[\eta_{sp.}/c]_{c\to 0}$ and $[(\log_e \eta/\eta_0)/c]_{c\to 0}$, where $\eta_{sp.}$ is the specific viscosity, η/η_0 the relative viscosity, and c the concentration in g. of polymer per 100 c.c. of solution (Staudinger and Fischer, *J. pr. Chem.*, **1940**, **157**, 19; **1941**, **157**, 58; Kraemer, *Ind. Eng. Chem.*, **1938**, **30**, 1200). At zero concentration both expressions give the limiting viscosity, but the latter expression, the intrinsic viscosity, was chosen for use because it was more nearly directly proportional to concentration at low concentrations and therefore allowed easier extrapolation to zero concentration at which the intrinsic viscosity becomes the limiting viscosity. The limiting viscosity (designated $[\text{I.V.}]_0$ below) was obtained by determining the relation of the viscosity of a solution of the polymer at two concentrations to that of the pure solvent at 20°, plotting $(\log_e \eta/\eta_{sol.})/c$ against c, and extrapolating to zero concentration. The concentrations were of the order of 0·5 and 0·25 g. of polymer per 100 c.c. of solution, the second concentration being obtained by dilution. The results are shown in Table II.

Table II.

Polymer.	$[\text{I.V.}]_{\eta_{sp.}}$	$[\text{I.V.}]_{\eta_{sp.}}$	$[\text{I.V.}]_0$	Mol. wt., osmotic.
Polyethylene adipate	0·304	0·296	0·312	10,000
,, + 1·0% P.E.	0·308	0·294	0·322	17,000
,, + 1·5% P.E.	0·327	0·312	0·342	25,000
,, + 1·8% P.E.	0·396	0·384	0·408	37,000
,, + 1·9% P.E.	0·448	0·439	0·457	47,500
,, + 2·0% P.E.	—	Gelled	—	—

P.E. = pentaerythritol.

(These polymers are identical with those described on p. 1616.)

When the limiting viscosity is plotted against the amount of pentaerythritol added, there is little increase in gradient up to 1·5% of added pentaerythritol, but additional amounts cause a very rapid increase in gradient. A plot of the limiting viscosity and molecular weight gives a curve whose gradient gradually increases with increasing molecular weight.

Copolymers of ethylene adipate with more pentaerythritol than is required to gel the melt on complete condensation gave another set of figures (Table III) whose limiting viscosity–molecular weight plot lay at a higher viscosity level than the polymers recorded in Table II.

As previously, the agreement between chemical and osmotic molecular weights was good, except in the cases of copolymers No. 2 and 4. These copolymers also show limiting viscosities which are out of all proportion to their molecular weights, and it is clear that the physical properties (*e.g.*, size and shape) of these copolymers have altered.

As shown before, the molecular weight can be determined chemically from the expression, $M = 56{,}000s/S$, where M is the molecular weight, s the number of hydroxyl groups per molecule, and S the

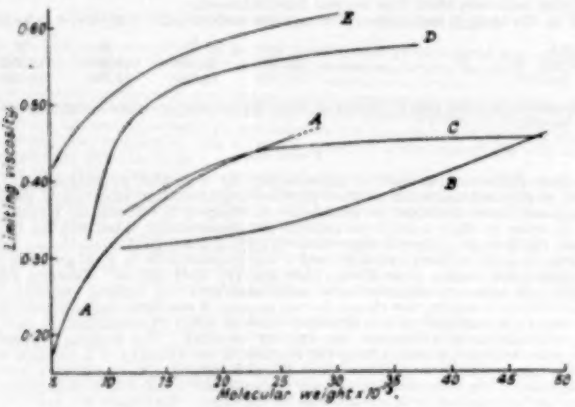
TABLE III.

Copolymer no.		$[I.V.]_{0\cdot33}$.	$[I.V.]_{0\cdot33}$.	$[I.V.]_0$.	Mol. wt., osmotic.
Ethylene adipate + excess of P.E.,	No. 1	0·345	0·233	0·356	10,000
" "	No. 2	0·542	0·539	0·545	19,500
" "	No. 3	0·374	0·368	0·379	15,500
" "	No. 4	0·661	0·657	0·665	20,000
" "	No. 5	0·388	0·378	0·399	17,000
" "	No. 6	0·446	0·444	0·448	23,000
" "	No. 7	0·448	0·439	0·457	47,500

(These polymers are identical with those in Table I.)

sum of the acetyl and acid values. By substituting the osmotic molecular weight for M, and the sum of acetyl and acid values for S, x can be calculated for these polymers: it is 7·75 and 6·80 for copolymers Nos. 2 and 4, respectively, so that these copolymers in fact possess more hydroxyl groups than do those which show average figures. This can be accounted for by the introduction of another pentaerythritol nucleus into some of the polymer molecules, which are therefore intermediate between the average polymer and the insoluble network. This view is supported by the fact that these anomalous copolymers dissolve with considerably greater difficulty than the normal copolymer.

FIG. 2.



(*A*) *Polyethylene adipate*
(*B*) " + *pentaerythritol.*
(*C*) " + *pentaerythritol.*
(*D*) " + *dipentaerythritol.*
(*E*) " + 1 : 1 : 1-*trishydroxymethylpropane.*

By omitting those two polymers and plotting limiting viscosity–molecular weight curves, it was shown that, as a whole, the curve lies above the curve plotted from Table II, tending to meet it only at the extreme ends (Fig. 2). It would appear that Table II gives values for copolymers in which cruciform molecules were in the process of being formed, or in fact, had been actually formed, but were diluted by the presence of linear polyethylene adipate present in the copolymer. It is highly probable that, since condensation had been carried out to the limit, a mixture of such molecules is, in fact, present.

On carrying out the same type of work on the excess dipentaerythritol copolymers, it was found that the limiting viscosities lay at a much higher level for corresponding molecular weights:

Copolymer.		$[I.V.]_{0\cdot33}$.	$[I.V.]_{0\cdot3}$.	$[I.V.]_0$.	Mol. wt., osmotic.
Ethylene adipate + excess of D.P.E.,	No. 1	0·545	0·539	0·551	27,500
" "	No. 2	0·563	0·558	0·568	23,000
" "	No. 3	0·517	0·511	0·523	15,500
" "	No. 4	0·489	0·480	0·498	13,700
" "	No. 5	0·461	0·455	0·467	14,000
" "	No. 6	0·442	0·432	0·452	10,800
" "	No. 7	0·356	0·350	0·362	9,300
" "	No. 8	0·338	0·328	0·348	8,000

D.P. = dipentaerythritol.

(These polymers are identical with those on p. 1616.)

The curve for limiting viscosity–molecular weight lies, as before, at a higher viscosity level, with much steeper initial slope, but the same limiting effect is apparent at higher molecular weights, the viscosity showing little increase with increasing molecular weight (Fig. 2). That the viscosity has been increased for corresponding molecular weights when compared with the curve given by Table II can be accounted for by the greater tendency of a molecule with six arms originating in one nucleus to become spherical.

Similar treatment of the 1 : 1 : 1-trishydroxymethylpropane series of copolymers gave the following figures:

Copolymer.		$[\text{I.V.}]_{0\cdot 25}$.	$[\text{I.V.}]_{0\cdot 35}$.	$[\text{I.V.}]_0$.	Mol. wt., osmotic.
Ethylene adipate + excess of T.M.P.,	No. 1	0·371	0·356	0·336	19,000
,,	No. 2	0·340	0·325	0·335	14,900
,,	No. 3	0·320	0·311	0·329	14,700
,,	No. 4	0·304	0·496	0·312	10,500
,,	No. 5	0·463	0·457	0·469	7,400

T.M.P. = trishydroxymethylpropane.
(These polymers are identical with those on p. 1617.)

The plot of molecular height and limiting viscosity in this series of polymers is even higher than those of the previous copolymers and lies roughly parallel to the curve obtained from the data in Tables II and III, but is slightly less steep in the low-molecular-weight region.

Discussion.

Any degree of branching in any polymer should be reflected in a lowering of the value of the branching coefficient α if the modified Staudinger equation (Huggins, *Ind. Eng. Chem.*, 1943, **35**, 980):

$$[\text{I.V.}]_0 = KM^{\alpha} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $[\text{I.V.}]_0$ is the limiting viscosity, K is a constant, and M the molecular weight, and where the values of α lie between zero for spheroid particles and approximately unity for linear polymers. This equation may be evaluated simultaneously to give a value for α in terms of two values of $[\text{I.V.}]_0$ and the corresponding values of M for any one polymer. In the case of linear polyethylene adipate over the range M = 5800—9500, α is 0·85, while for the pentaerythritol copolymer over the range M = 11,000—48,000 it is 0·17, for the dipentaerythritol copolymer over the range M = 10,000—30,000 it is 0·28, and for the trishydroxymethylpropane copolymer for M = 10,000—30,000 it is 0·16. In all the copolymers (*i.e.*, excepting ethylene adipate alone), there was a tendency for the value of α to become very low at molecular weights higher than those cited.

These values are not strictly comparable but show that definite structural changes have taken place within the polymer meolcule which have had the effect of reducing α to a considerably lower figure than that of the linear polymer. The limiting value of α is that postulated by Einstein for spherical particles (*Ann. Physik*, 1906, **19**, 289; 1911, **34**, 591), *viz.*:

$$[\text{I.V.}]_0 = 2{\cdot}5 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

which can be written in a form comparable with equation (1), *viz.*:

$$[\text{I.V.}]_0 = 2{\cdot}5M^0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

From this it can be seen that the more spherical a molecule becomes, the more the value of α tends to zero, and the more should the limiting value of the viscosity tend towards 2·5. From the above figures, the various copolymers appear to show a definite tendency towards the formation of spheroid molecules, although it is hardly to be expected that equation (3) would be obeyed, as such copolymer molecules are in fact open structures in which the arms assume a more or less extended shape depending on the solvent power of the medium used.

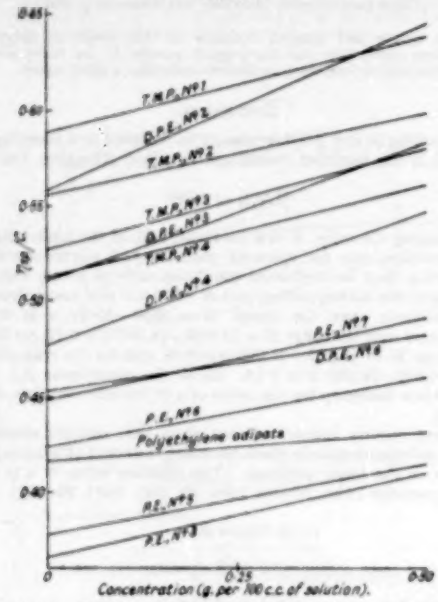
Again, with regard to the shape of the various copolymer molecules, it can be seen that a molecule possessing six arms emanating from one nucleus will have a greater tendency towards a spherical shape than one possessing only four. Thus it is to be expected that the dipentaerythritol copolymers will have a higher viscosity level than pentaerythritol copolymers. Again it is reasonable to expect that a molecule such as the trishydroxymethylpropane copolymers, where two nuclei are present, should exert less steric effects, and therefore less restriction on the mobility of the arms; it will consequently approximate more closely to a spherical particle in solution, and should therefore lie at a higher viscosity level than either of

the other copolymers. These relative viscosity levels, however, depend to a considerable extent on solubility, as can be seen from the following table for polymers dissolved in *o*-chlorophenol:

	$[I.V.]_{0\cdot 25}$.	$[I.V.]_{0\cdot 33}$.	$[I.V.]_0$.	Mol. wt.
E.A. + T.M.P., No. 2	0·751	0·725	0·777	14,900
E.A. + D.P.E., No. 4	0·610	0·601	0·619	13,700
E.A. + P.E., No. 5	0·602	0·594	0·620	15,500

It will be seen that, in *o*-chlorophenol, the limiting viscosities are considerably higher. To find out the relative solubilities of these polymers in *o*-chlorophenol and chloroform, solutions (0·5 g./100 c.c. of solution) of one polymer (E.A. + T.M.P., No. 3) were treated with methyl alcohol, in which the polymer is insoluble, till turbidity appeared in the solution. For 10 c.c. of the *o*-chlorophenol solution 31·2 c.c. of methyl alcohol were required, and for the chloroform solution only

FIG. 3.



P.E. = *pentaerythritol*. *D.P.E.* = *dipentaerythritol*. *T.M.P.* = *trishydroxymethylpropane*.

15·0 c.c. The solubility in *o*-chlorophenol is therefore much greater than in chloroform. The increase in solubility is accompanied by an increase in viscosity (Alfrey, Bartovics, and Mark, *J. Amer. Chem. Soc.*, 1942, **64**, 1557). This is accounted for by the fact, that, since the viscosity has increased, the field in which the flexible arms of the molecule can move has also increased because of the greater penetrative power of the solvent towards the nucleus of the molecule. The arms therefore become more extended in a good solvent, resulting in an increase in viscosity.

To discover whether any such solubility effect could account for the varying viscosity levels of the copolymers, representative solutions (0·5 g./100 c.c. of solvent) of polymers (mol. wt. = about 10,000) were titrated with methyl alcohol to the turbidity point, with the following results:

Polymer.	Mol. wt.	MeOH, c.c.
E.A.	10,000	17·5
E.A. + P.E., No. 1	10,000	16·3
E.A. + D.P.E., No. 7	9,300	16·6
E.A. + T.M.P., No. 4	10,500	17·0

It will be seen that polyethylene adipate is the most soluble and that the copolymers show little difference. It is therefore unlikely that solubility effects can account for the variation in viscosity levels, which must therefore be entirely due to differences in structure.

Further interesting information is afforded by an investigation into the viscosities obtained for the various copolymers from the point of view of the Huggins equation, modified to allow of its use in polymer solutions by the introduction of the Huggins constant; this constant depends on the size, shape, and inter-attractive properties of solute and solvent molecules. The equation in its more general form is

$$\eta_{sp}/c = [\eta](1 + K\eta_{sp})$$

where η_{sp} is the specific viscosity, $[\eta]$ is the limiting viscosity, and K the Huggins constant, and holds at low concentrations (Huggins, *J. Physical Chem.*, 1938, **42**, 911; 1939, **43**, 439; *J. Amer. Chem. Soc.*, 1942, **64**, 2716).

With rod-like molecules, *e.g.*, linear polyesters, interference between molecules would be expected to be low, so η_{sp}/c would also be low, while the introduction of branching would incline the molecule to a more spherical shape, with a resultant increase in mutual interference between molecules. It is therefore reasonable to expect that the slope of the curve obtained on plotting η_{sp}/c against c would increase with the introduction of a more spherical molecule built up by means of branches. Little work has been done to support this theory, but figures obtained for amylopectin and amylose appear to agree with these postulates (private communication from Imperial Chemical Industries Limited, Dyestuffs Division).

To test this theory, various copolymers from each series were evaluated for η_{sp}/c from the data used for evaluation of limiting viscosities. The figures were obtained as follows (the slope of the line to the concentration axis is given by tan θ) (Fig. 3):

Polymer.	η_{sp}/c.	η_{sp}/c.	η_{sp}/c.	tan θ.	Mol. wt.
E.A. + P.E., No. 3	0·388	0·410	0·366	0·22	14,000
,, No. 5	0·396	0·415	0·377	0·19	15,500
,, No. 6	0·442	0·461	0·423	0·19	23,000
,, No. 7	0·470	0·492	0·448	0·22	47,500
E.A. + D.P.E., No. 2	0·602	0·647	0·557	0·45	42,000
,, No. 3	0·547	0·584	0·510	0·37	20,000
,, No. 4	0·512	0·547	0·477	0·35	13,700
,, No. 6	0·468	0·483	0·453	0·18	11,000
E.A. + T.M.P., No. 1	0·614	0·640	0·588	0·26	23,000
,, No. 2	0·578	0·600	0·556	0·22	15,200
,, No. 3	0·554	0·581	0·527	0·27	13,300
,, No. 4	0·537	0·562	0·512	0·25	10,200
Linear E.A.	0·424	0·432	0·416	0·08	20,000

From a consideration of these figures, information on the shape of the molecule may be obtained. Since K, the Huggins constant, and hence tan θ are shape factors, variations will reflect an alteration in the structural shape of the molecule, and, if the possibilities mentioned before are taken into consideration, linear molecules ought to show a low value of tan θ, and any tendency towards formation of spherical molecules should be shown by an increase in the value of tan θ. As shown above, linear polyethylene adipate has a value of 0·08, pentaerythritol copolymers have an average of 0·20, and trishydroxymethylpropane copolymers 0·25, whereas dipentaerythritol copolymers show a much greater increase, to 0·35.

As mentioned above, K (and hence tan θ) is essentially a shape factor bound up with the inherent shape of the molecule itself and of the effect of solvents on the shape which the molecule assumes in solution. Branching changes a molecule which is linear and possesses little or no mutual interference in dilute solution into a molecule which is more inclined to a spherical shape and, because of its extensible arms, has greater possibilities of mutual interference. The increase in the value of tan θ from 0·08 for linear polyethylene adipate to 0·20 for the pentaerythritol copolymer is thus explained. Since there is little difference in the solubilities of polyethylene adipate and its copolymers, solubility can have little bearing on tan θ.

The slight but definite difference in the value of tan θ for the trishydroxymethylpropane copolymer cannot be attributed to the variation in solubility, and must arise from structural considerations alone. Both this and the pentaerythritol copolymer contain, on the average, four hydroxyl groups per molecule, and it is evident that the molecules must differ considerably in structure. Only one pentaerythritol nucleus is required to give four end groups, but for trishydroxymethylpropane two such nuclei are necessary, so that the molecule must take up a "double-Y" shape, two arms extending from each end of the linear portion of the molecule.

The field covered by such a molecule in the "kinked" position will be larger for comparable molecular weights, although it may not attain a completely spherical shape. Since the field is larger, the mutual interference must be greater, the result being a small but definite increase in the value of the Huggins constant and consequently in tan θ.

From a consideration of the relative limiting viscosities at corresponding molecular weights, it can be seen that the trishydroxymethylpropane copolymer has a greater claim to being considered spherical since it tends more to the limiting value of 2·5 (as given by the Einstein equation), evaluated for rigid spheres in suspension and in such dilution that inter-attractive forces are negligible. A molecule with two pairs of extended arms originating at each end of a linear polymer chain has an even greater possibility for mutual interference than a polymer in which four arms extend from a central nucleus, and in addition possesses less steric effects within itself.

In considering the dipentaerythritol copolymer, one can visualise the reason for the increase in tan θ where six arms are present in place of four. Such a molecule would have a considerably greater opportunity for mutual interference, but at the same time must be severely restricted in the movements of its arms by steric forces which are bound to be present when six arms emanate from one nucleus. For this reason, the value of tan θ is considerably higher than for the other two polymers, but on account of steric factors this polymer is unable to form as spherical a field as the trishydroxymethylpropane copolymer.

From these observations, it will be seen that viscosity data, as applied to the Huggins equation incorporating the shape factor K, are helpful in determining the degree of branching in polymers of approximately similar structure, although structural differences in "isomeric" molecules will alter the values of K slightly. From the observations above, it would appear that there is no correlation between the value of the shape factor K (or tan θ) and the limiting viscosity.

One of us (G. W. Y.) is indebted to the Carnegie Trust and Imperial Chemical Industries Limited, Plastics Division, for making it possible to participate in this work. We are also grateful to Imperial Chemical Industries Limited, Dyestuffs Division, for the provision of some of the compounds used.

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335. *The Reaction of Fluorine with the Oxides and Oxy-compounds of Manganese and Rhenium.*

By E. E. AYNSLEY, R. D. PEACOCK, and P. L. ROBINSON.

Potassium permanganate and the oxides of manganese on reaction with fluorine yield manganese trifluoride contaminated with a little manganese difluoride. No oxyfluoride of manganese is produced in these reactions. Rhenium dioxide and potassium per-rhenate give two new oxyfluorides, rhenium oxypentafluoride, $ReOF_5$, and rhenium dioxytrifluoride, ReO_2F_3. That the highest fluoride of rhenium is ReF_7 has been confirmed. No evidence has been obtained of the previously reported oxyfluorides $ReOF_4$, ReO_2F_5, ReO_2F, and $ReOF_3$.

MANGANESE difluoride prepared by Berzelius (*Pogg. Ann.*, 1824, **1**, 24, 197), and manganese trifluoride, prepared by Moissan (*Compt. rend.*, 1900, **130**, 622), are well known. Wohler claimed to have isolated MnO_3F but his product is now believed to have been a mixture of potassium permanganate and fluoromanganite contaminated with silicon fluoride and we are left without reliable evidence for or against the existence of an oxyfluoride of manganese.

Ruff and Kwasnik (*Z. anorg. Chem.*, 1932, **209**, 113; 1934, **219**, 65) reported the preparation of rhenium hexafluoride and tetrafluoride, and claimed to have prepared rhenium oxytetrafluoride, $ReOF_4$, and rhenium dioxydifluoride, ReO_2F_2, by (*a*) the interaction at laboratory temperature of rhenium hexafluoride and silica, and (*b*) the action of a mixture of oxygen and fluorine on rhenium at 125—300°. Moreover, in the products from the interaction between rhenium hexafluoride, potassium fluoride, hydrogen fluoride, and fluorine in a silica vessel, they claimed to have found indications of rhenium oxydifluoride, $ReOF_3$, and rhenium trioxyfluoride, ReO_3F, although these were not isolated.

We describe the reactions between elementary fluorine, diluted with nitrogen, and manganous oxide, trimanganic tetroxide, manganese dioxide, potassium permanganate, rhenium dioxide, and potassium per-rhenate. In addition, we have repeated the work previously reported on the fluorides and oxyfluorides of rhenium.

Manganous oxide and trimanganic tetroxide begin to react with fluorine just below 100° and continue to do so with incandescence. The product from both oxides is mainly manganese trifluoride carrying a trace of manganese difluoride. Manganese dioxide begins to react at 150° and gives the same product. Although looked for, no oxyfluoride of manganese was found in the residue from these experiments: the only volatile products were silicon fluoride from the glass and traces of hydrogen fluoride.

Potassium permanganate begins to react at about 150° and continues with sparks and incandescence. No trace was found of any oxyfluoride of septavalent manganese, and the residue was mainly a mixture of manganese trifluoride and potassium fluoride with a little manganese difluoride. No volatile manganese compound was formed, indicating the probable absence of potassium fluoromanganite, K_2MnF_6, which volatilises when heated.

The reaction with rhenium dioxide starts at 100° and continues with incandescence (*cf.* MnO_2). From this reaction two hitherto unknown oxyfluorides of rhenium, *viz.*, the *oxypentafluoride*, $ReOF_5$, and the *dioxytrifluoride*, ReO_2F_3, in which rhenium exhibits its maximum valency, have been prepared.

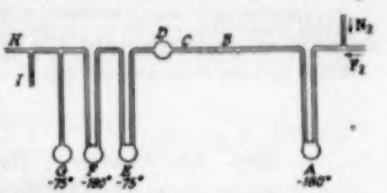
Potassium per-rhenate begins to react with fluorine at about 100°, melts with the heat of the reaction, and becomes yellow. The products are the same two new compounds, together with a residue of potassium fluoride.

In all these reactions no oxygen compound with fluorine could be detected, which suggests that in some of these reactions, *e.g.*, that involving MnO, oxygen is first liberated during the fluorination.

No evidence has been obtained of rhenium heptafluoride in the fluorination of metal, oxide, per-rhenate, or the hexafluoride, and the finding of Ruff and Kwasnik (*loc. cit.*) that the highest fluoride of rhenium is ReF_6 is confirmed. At temperatures above 300° rhenium hexafluoride undergoes disproportionation in contact with silica to yield traces of rhenium tetrafluoride. Contrary to their findings, however, pure rhenium hexafluoride does not react with silica at ordinary temperatures, nor does the reaction between rhenium, fluorine, and oxygen yield the oxyfluorides $ReOF_4$ and ReO_2F_3. The latter reaction has been carried out in vessels of Pyrex glass, nickel, and fluorite, and in each case the main reaction products were the oxypentafluoride and dioxytrifluoride. Furthermore, there were no indications of the trioxyfluoride, ReO_3F, or the oxydifluoride, $ReOF_3$, following the interaction of fluorine with a mixture of rhenium, potassium fluoride, and hydrogen fluoride in a silica vessel.

Experimental.

(a) *Manganese Compounds.*—The compounds to be fluorinated were dried by gently heating them in a vacuum for several hours. The reaction vessel was of Pyrex, and a mixture of fluorine and nitrogen (20 : 80, by vol.) was passed over the manganese compound at the rate of about 5 l. per hour. A liquid-air trap was inserted in the apparatus before the reaction vessel to remove traces of hydrogen fluoride. A series of three such traps was used to retain volatile products. Manganese trifluoride was principally produced (Found, in product from fluorination of manganese oxide: Mn, 49·9; F, 50·2. Calc. for MnF_3: Mn, 49·1; F, 50·9%). The small amount of manganese fluoride always present accounts for the slightly low fluorine values.



(b) *Rhenium Compounds.*—Anhydrous rhenium dioxide was prepared by dissolving the metal in dilute hydrogen peroxide and boiling the solution to give per-rhenic acid. This was then reduced with zinc dust and hydrochloric acid, giving a precipitate of black, hydrated dioxide, $ReO_2.2H_2O$. After being collected in a sintered-glass crucible and washed with hydrochloric acid and water, it was dried at 110°. The product was then transferred to a silica tube which was attached to a drying train and Hyvac pump, and the oxide was completely dehydrated by heating the silica tube for 6 hours at 350° under constant evacuation. Any trace of rhenium heptoxide, Re_2O_7, present was removed by sublimation, a small luminous Bunsen flame being used.

The apparatus of Pyrex (see figure) was first swept clear of air with pure nitrogen, and the above fluorine–nitrogen mixture was streamed through at a rate of 5 l. per hour. Any trace of hydrogen fluoride was removed in *A*. No reaction occurred at room temperature but at about 100° the dioxide took fire and burned with the evolution of copious white fumes. It was found convenient, in view of the heat of the reaction, to divide the charge of dioxide into several small portions, each in a separate depression in the reaction vessel. Starting at the end nearest *C*, each portion was separately raised to the reaction temperature. The more volatile products collected in *E* and *F*, and the less volatile in *D*. When the reaction was finished, the fluorine was displaced by nitrogen, and the apparatus sealed at points *C* and *H*, evacuated *via I*, and finally sealed off at this point. In previous experiments attempts were made to fractionate the two substances but all the evidence pointed to the original separations being

effective. The volatile products in *E* and *F* were sublimed into the vapour-density bulb *G*, which was cooled to −75°. Any silicon tetrafluoride (sublimes at −90°) present was then removed by cooling *E* or *F* to −180°; *G* and *D* were sealed off, and their contents analysed.

(*a*) The fraction in *G* (Found: Re, 62·8; F, 31·9%; *M*, 300·7. $ReOF_4$ requires Re, 62·7; F, 32·0%; *M*, 298·2) was ***rhenium oxypentafluoride***. At room temperature it is a cream-coloured crystalline solid, which melts to an almost colourless liquid at 34·5°, and boils at 55°/760 mm. Its liquid density is 3·8 at 40° and its solid density is 4·2 at the m. p. In the absence of moisture it does not attack glass at ordinary temperatures if it is free from hydrogen fluoride. It gives white fumes when exposed to moist air, and dissolves in water with hissing, forming a colourless solution containing per-rhenic acid and hydrofluoric acid, $ReOF_4 + 3H_2O = HReO_4 + 5HF$. In the presence of water hexavalent rhenium would have given a black precipitate of hydrated rhenium dioxide $ReO_2,2H_2O$, *viz.*, $3Re^{6+} = 2Re^{7+} + Re^{4+}$. This rules out the possibility of our compound being a mixture of rhenium hexafluoride and oxytetrafluoride, $ReOF_4$, and points significantly to its being the oxypentafluoride, $ReOF_3$. The oxyfluoride is readily reduced (cf. ReO_2F_3 below) to Re^{4+} by traces of organic matter.

(*b*) The fraction in *D* (Found: Re, 67·0; F, 20·5. ReO_2F_3 requires Re, 67·7; F, 20·7%) was ***rhenium dioxytrifluoride***. At room temperature it is a pale yellow powder, which begins to sinter at 90° and is definitely liquid at 95°. The vapour density at this temperature is appreciable and the compound can be distilled without decomposition in a luminous Bunsen flame at 200°. The distillate was homogeneous and each successive fraction had a composition corresponding to the formula ReO_2F_3. The liquid solidifies to a glass but the compound can be obtained crystalline by slow sublimation *in vacuo*. ReO_2F_3 does not attack glass below about 200°, and it is deliquescent in moist air. It dissolves in water to form a colourless solution containing per-rhenic acid and hydrofluoric acid, showing the presence of Re^{VII} only: $ReO_2F_3 + 2H_2O = HReO_4 + 3HF$. Unlike $ReOF_4$, it is only slowly reduced by traces of organic matter to quadrivalent rhenium. In this preparation the two oxyfluorides are produced in the proportions of about 1 part of $ReOF_4$ to 3 parts of ReO_2F_3.

Potassium per-rhenate was fluorinated in the same type of apparatus and reaction was found to begin at 160°. Under the same experimental conditions as that used for ReO_2 the same two oxyfluorides were formed in the ratio of about 1 part of $ReOF_4$ to 10 parts of ReO_2F_3.

The fluorination of rhenium metal at about 125° produced a pale yellow solid exactly resembling custard-powder in appearance. It had m. p. 19° and b. p. 48° and was identified as ReF_4 (Found: Re, 62·0; F, 38·7%; *M*, from vapour-density determination, 302·0. Calc. for ReF_4: Re, 62·0; F, 38·0%; *M*, 300·3). This is in agreement with the findings of Ruff and Kwasnick (*loc. cit.*), who were also unable to prepare a fluoride of rhenium containing more than six atoms of fluorine.

Attempts to repeat those authors' work on the oxyfluorides of rhenium were made on the following lines. (1) Fluorine (75 parts) and oxygen (25 parts), together with a little nitrogen to act as a carrier gas, were passed over rhenium. Vessels used were Pyrex glass, nickel, and fluorite. (2) Rhenium hexafluoride was sealed up in a quartz bulb and left for several weeks at room temperature. (3) A fluorine–nitrogen stream was passed over a heated mixture of rhenium and potassium hydrogen fluoride ($KF,2HF$) in a silica vessel. In (1) the new compounds described above were obtained, the primary product being rhenium oxypentafluoride, $ReOF_5$, and in (2) no reaction took place. In (3) a blue-black complex residue was obtained from which no oxyfluoride of rhenium could be isolated. It was found that above 300° rhenium hexafluoride reacts with quartz yielding minute quantities of a dark green-blue solid agreeing with the description given by Ruff and Kwasnik (*loc. cit.*) for rhenium tetrafluoride, but the quantities were too small for confirmatory analysis.

The authors express their indebtedness to the General Chemicals Division of Imperial Chemical Industries Limited, Runcorn, for the fluorine cell used, and to King's College for a Post-Graduate Studentship, which enabled one of them (R. D. P.) to take part in the work.

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336. *The Kinetics of Halogen Addition. Part XVI. αβ-Ethylenic Acids.*

By D. A. EVANS, T. R. WATSON, and P. W. ROBERTSON.

Certain new compounds have been investigated, and rates of electrophilic halogen addition compared, *viz.*:

$CHEt{:}CH{\cdot}CO_2H > CHMe{:}CH{\cdot}CO_2H$; *cyclo*-$C_5H_8{:}CH{\cdot}CO_2H \sim$ *cyclo*-$C_6H_{10}{:}CH{\cdot}CO_2H$;
$CH_2{:}CMe{\cdot}CO_2R > CH_2{:}CH{\cdot}CO_2R$; $CHMe{:}CMe{\cdot}CO_2H > CHMe{:}CH{\cdot}CO_2H$;
$CHPh{:}CH{\cdot}CO_2H > CHPh{:}CMe{\cdot}CO_2H > CHPh{:}CPh{\cdot}CO_2H$; $CBrPh{:}CH{\cdot}CO_2H >$
$CHPh{:}CBr{\cdot}CO_2H$; $CHPh{:}CH{\cdot}CO_2H > p\text{-}C_6H_4Cl{\cdot}CH{:}CH{\cdot}CO_2H > o\text{-}C_6H_4Cl{\cdot}CH{:}CH{\cdot}CO_2H$;
$CHPh{:}CH{\cdot}CO_2H < CHPh{:}CH{\cdot}CH{:}CH{\cdot}CO_2H$ (γδ-addition) $> CHPh{:}CH{\cdot}CH{:}C(CO_2H)_2$ (γδ-addition) $> CHPh{:}C(CO_2H)_2$.

Also certain nucleophilic rates of bromine addition in the presence of hydrogen bromide have been compared, *viz.*: $CH_2{:}CH{\cdot}CO_2R > CH_2{:}CMe{\cdot}CO_2R$; $CHPh{:}CH{\cdot}CH{:}C(CO_2H)_2$ (αβ-addition) $\sim CHPh{:}C(CO_2H)_2$.

CERTAIN αβ-unsaturated acids have already been investigated and their kinetics of halogen addition discussed in earlier papers in this series; they include acrylic, crotonic, and ββ-di-

methylacrylic acids, cinnamic acid and its methyl and nitro-derivatives, and the dibasic acids, maleic, fumaric, citraconic, mesaconic, glutaconic, and β-methylglutaconic (*J.*, 1945, 129, 891). The carboxyl group, by its combined inductive and tautomeric effects, has a deactivating influence on electrophilic reactivity, but, on the other hand, if the electronic flow towards the ethylenic link is not considerable, it can cause compounds to react by the nucleophilic mechanism, for example when hydrogen tribromide is the reagent. It is inferior to the more strongly electron-attracting aldehyde group, which in general confers on compounds a lower electrophilic and a higher nucleophilic reactivity (*J.*, 1945, 888). These investigations are now extended to include certain other αβ-unsaturated acids, which have been examined for special reasons. The velocities quoted are second-order rate coefficients, k_2 (min.$^{-1}$ g.-mol.$^{-1}$ l.).

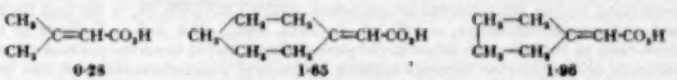
β-Methyl- and β-Ethyl-acrylic Acids.—These compounds were compared with reference to the relative effectiveness of the electron-contributing alkyl groups. The following rates were found for electrophilic bromine addition in 25% aqueous acetic acid solution at 25°, the reactants being M/40 :

	$CHMe:CH\cdot CO_2H$.	$CHEt:CH\cdot CO_2H$.
k_2	0·74	1·1
k_2 (+ M/5-H_2SO_4)	0·62	0·92

Owing to the slight dissociation of the acids in the mixed solvent the rates are increased as a result of the superior reactivity of the unsaturated anion (cf. *J.*, 1937, 341). Sulphuric acid represses this ionisation, and the rates for the undissociated acids are thus obtained. The relative reactivities due to the two alkyls, Et 1·5 times Me, may be compared with the values for the alkylbenzenes for chlorination, Me 1·2 times Et (*J.*, 1943, 279), and the values for phenyl ethers, Et twice Me (cf. Bradfield and Jones, *Trans. Faraday Soc.*, 1941, 37, 743). In this last mode of reaction, *i.e.*, in a compound such as anisole, an inductive effect only is possible, and in the other two reactions combined inductive and hyperconjugation effects are in operation. In the alkylacrylic acids the inductive effect is relatively more important than hyperconjugation, and the reverse is true for the alkylbenzenes. This is in accordance with expectation as the inductive effect is short-range and should therefore operate more powerfully in an ethylene than in a larger benzene molecule. A similar conclusion has been reached from measurements of the electronic spectra of ethylenic and aromatic hydrocarbons (for discussion, cf. Walsh, *Annual Reports*, 1947, 32).

The nucleophilic rates of the two acids were also measured, reactants being M/40 with M/5-hydrogen bromide at 25° : for β-ethylacrylic acid $k_2 = 0{\cdot}073$, and for β-methylacrylic acid $k_2 = 0{\cdot}054$, in acetic acid solution. The reactivities remain in the electrophilic order, as sometimes happens (cf. *J.*, 1945, 888 : 1948, 980), since the two stages of the nucleophilic reaction have opposing electronic requirements.

cyclo*Pentylidene- and* cyclo*Hexylidene-acetic Acids.*—These two compounds were examined as part of a more general investigation of the influence of steric factors on the rate of halogen addition. Rates of bromine addition were measured in acetic acid at 25°, and are now given as second-order coefficients for M/40-reactants :



k_2 ($x = 50$)	0·28	1·65	1·96

There is therefore no evidence that halogenation of these compounds is sterically hindered. A corresponding difference, indicating also a greater electron-repelling power of the cyclic group than of ββ-dimethyl, is shown by reference to the dissociation constants : *cyclo*hexylideneacetic acid, $K = 0{\cdot}26 \times 10^{-4}$; dimethylacrylic acid, $K = 2{\cdot}2 \times 10^{-4}$.

Acrylic and α-Methylacrylic Esters.—These compounds were examined to discover the influence of the α-methyl group on the electrophilic and nucleophilic rates, which were measured in acetic, acid solution at 25°.

	$CH_2:CH\cdot CO_2Et$.	$CH_2:CMe\cdot CO_2Me$.*
k_2 (Cl_2)	0·056	3·4
k_2 (HBr_2)	0·42	0·165

* Me and Et esters of other αβ-unsaturated acids show only slightly differing rates.

An approximately 60-fold increase in velocity is caused by the α-methyl group, and the order of the nucleophilic is the reverse of that of the electrophilic reactivity, as similarly found for related compounds (*J.*, 1945, 129).

Crotonic and Tiglic Acids.—For these two compounds also the influence of an α-methyl group is to cause a considerable (60-fold) increase in the electrophilic rate of chlorine addition in acetic acid at 25° :

	CHMe:CH·CO_2H.	CHMe:CMe·CO_2H.
k_2 (Cl_2)	0·62	36
k_2 (Br_2) (+ LiBr)	0·069	0·22

The bromine rates are for M/40-reactants, with M/40-sodium acetate and M/10-lithium bromide, and are less spaced than the values for chlorine addition owing to a contribution from a nucleophilic rate in the crotonic acid reaction.

Cinnamic Acid, its α-Methyl and α-Phenyl Derivatives.—The rates of chlorine addition have been measured in acetic acid at 25°.

	CHPh:CH·CO_2H.	CHPh:CMe·CO_2H.	CHPh:CPh·CO_2H.
k_2	5·0	3·0	0·36

The influence of the α-methyl group, in contrast with that for the preceding compounds, is to reduce the electrophilic rate. The methyl thus acts as if it lessened the $+T$ influence of the phenyl. The α-phenyl group would be expected to act in a similar manner and, as it also exerts a $-T$ effect in this position, the rate for α-phenylcinnamic acid is lower than that of α-methylcinnamic acid.

α- and β-Bromocinnamic Acids.—When attached to an ethylenic carbon atom, a halogen may exert a $+T$, $-I$ effect as in a compound such as $CHBr{:}CH_2$, or a $-I$ effect only, when the electrophilic attack is on the carbon to which the halogen is attached, as in CHPh:CHBr. The deactivating influence of the bromine atom in such compounds is considerable, and there is a large rate reduction in comparison with the unsubstituted compound. Similar effects are apparent with the two compounds now under consideration, although the deactivation is smaller; the following are rates of chlorine addition in acetic acid at 25° :

	CHPh:CH·CO_2H.	CBrPh:CH·CO_2H.	CHPh:CBr·CO_2H.
k_2	5·0	0·21	0·0077

p- and o-Chlorocinnamic Acids.—The following rates of chlorine and bromine addition have been measured in acetic acid at 25°; in the bromine additions the reactants were M/40, with M/40-sodium acetate, and in the catalysed reactions, the lithium bromide was at M/10 :

	CHPh:CH·CO_2H.	*p*-C_6H_4Cl·CH:CH·CO_2H.	*o*-C_6H_4Cl·CH:CH·CO_2H.
k_2 (Cl_2)	5·0	2·5	0·27
k_2 (Br_2)	0·080	0·036	0·0041
k_2 (Br_2) (+ LiBr)	0·074	0·045	0·014

The electrophilic rates of chlorine addition may be compared with the rates, under the same conditions, of the benzylideneacetophenones, CHPh:CH·COPh ($k_2 = 60$) and its *p*- ($k_2 = 23$) and *o*-chloro-derivatives ($k_2 = 1·8$) (cf. *J.*, 1948, 980). The $+T$, $-I$ effects of the chlorine atom tend to balance each other in the *para*-position, but in the *ortho*-position the deactivating influence of the chlorine becomes superior. Similarly *o*-nitrocinnamic acid was found to add chlorine at a slower rate than did its *para*-isomer (*J.*, 1945, 891). As the second stage of halogen addition involves a Walden-like inversion, it was suggested that there might be a steric effect in such cases. There is, however, gradually accumulating evidence that such steric hindrance does not operate in these reactions.

The rates of bromine addition in the presence of sodium acetate are in the same ratio as the rates of chlorine addition, *i.e.*, the reactions with bromine also proceed by the electrophilic mechanism. Whereas lithium bromide reduces the rate for cinnamic acid (the catalytic effect of the Br^- ion being obscured by $LiBr_3$ formation), it causes an increase in rate for the chlorocinnamic acids, in which compounds the chlorophenyl group exerts a $-I$ as well as a $+T$ effect. According to the classification of modes of catalysis by electrolytes in acetic acid solution (*J.*, 1949, 294), cinnamic acid belongs to Class I, and the chlorocinnamic acids to Class II, and for all three compounds lithium chloride is found to be superior to lithium bromide as a catalyst.

Cinnamylidene-acetic and -malonic Acids.—The rates of bromine addition to these two compounds are compared with the values for cinnamic and benzylidenemalonic acids, reactants

being M/80 in the presence of sodium acetate to eliminate any acid-catalysed nucleophilic addition, in acetic acid at 25°:

	$CHPh{=}\overset{\gamma}{C}H{\cdot}CH{=}CH{\cdot}CO_2H$. (I.)	$CHPh{=}\overset{\gamma}{C}H{\cdot}CO_2H$. (II.)
k_2 ($x = 20$)	200	0·040
	$CHPh{=}\overset{\gamma}{C}H{\cdot}CH{=}C(CO_2H)_2$. (III.)	$CHPh{=}\overset{\gamma}{C}(CO_2H)_2$. (IV.)
k_2 ($x = 20$)	0·42	~0·0004

The great reactivity of (I) compared with (II), and of (III) as compared with (IV), suggests that, in the compounds (I) and (III), electrophilic attack is initiated, as shown by the arrows, at the γ- rather than at the α-position, as found for the related compound $CHMe{:}CH{\cdot}CH{:}CH{\cdot}CO_2H$ by Ingold *et al.* (*J.*, 1934, 79). The claim by Hinrichson (*Annalen*, 1904, **336**, 168) that αβ-addition takes place with (III) seems to be based on insufficient evidence. The latter compound is less reactive than (I) because of the combined effect of the two carboxyl groups attached to the same carbon atom, and this deactivation becomes still greater in (IV).

In the presence of hydrogen bromide, nucleophilic reactions will proceed; but in compounds (I) and (II) their contribution is relatively small, especially in the case of (I), for which the electrophilic reaction, although reduced in rate somewhat by hydrogen bromide, is very rapid. For (III) [k_2 (HBr_3) = 44] and (IV) [k_2 (HBr_3) = 28), however, owing to the increased electron-attracting power of the two carboxyl groups acting in concert, the nucleophilic reactions become dominant. Since the phenyl group hinders nucleophilic attack on an adjacent carbon atom, and since the tautomeric effect of the carboxyl groups will become weakened by transmission through the CH:CH group, the initial nucleophilic attack on (III) is probably on the β- rather than on the δ-position. The use of different reagents might, therefore, enable the isolation of αβ- and γδ-addition products with bromine, but actually there are complications owing to secondary changes. On bromine addition in the presence of hydrogen bromide, the product was the compound $CHPh{:}CH{\cdot}CH{:}CBr{\cdot}CO_2H$, formed by loss of carbon dioxide and elimination of hydrogen bromide; in the presence of sodium acetate, the γδ-addition product is accompanied by the bromoacetate formed by the intervention of solvent molecules in the final (non-rate-determining) stage of electrophilic addition. However, Hinrichson (*loc. cit.*) has shown that there is γδ-addition to the ester in an aprotic solvent.

Experimental.

The following compounds were used in this investigation: α-methylcinnamic acid, m. p. 82°; α-phenylcinnamic acid, m. p. 172°; crotonic acid, m. p. 72°; tiglic acid, m. p. 64°; methyl crotonate, b. p. 121°/760 mm.; methyl α-methylacrylate, b. p. 100°/755 mm.; β-ethylacrylic acid, m. p. 8°, b. p. 106°/17 mm.; *cyclo*hexylideneacetic acid, m. p. 90—91°; *cyclo*pentylideneacetic acid, m. p. 52°; α-bromocinnamic acid, m. p. 128°; β-bromocinnamic acid, m. p. 134°; *o*-, m. p. 200°, and *p*-chlorocinnamic acid, m. p. 243°; cinnamylideneacetic acid, m. p. 165°; cinnamylidenemalonic acid, m. p. 208°.

As small differences in reactivity were involved for crotonic and β-ethylacrylic acids and the latter compound is liable to be contaminated with the very much more highly reactive βγ-unsaturated isomer, a special check was made on the purity of the β-ethylacrylic acid. After purification by the method given by Sudborough and Thomas (*J.*, 1911, 2314) and several recrystallisations from light petroleum, the liquid sample was cooled until about half had crystallised; the solid and the liquid fraction on separation had identical m. p.s. Similarly the purity of the *cyclo*pentylidene- and *cyclo*hexylidene-acetic acids (which likewise tend to be contaminated with more reactive isomers) was especially tested. The purified specimens were crystallised from light petroleum, and after separation of the crystals the filtrate was evaporated to dryness; the two samples thus obtained had identical rates.

All measurements were made in duplicate in tightly stoppered bottles protected from light. Volatility corrections were applied to all chlorine reactions as previously described. The following are details of one of the measurements:

M/40-Tiglic acid + M/40-Br_2 + M/40-NaOAc in acetic acid at 25°; 1-ml. samples were titrated with M/80-sodium thiosulphate.

Time (mins.)	0	32·75	99·5	219·5;	0	17	66·3	197
Titre (ml.)	4·01	3·47	2·73	2·06;	4·01	3·73	3·04	2·12

From the separate curves: $x = 20$, $t = 54·5$; $x = 20$, $t = 56$.

Additional results are expressed as times (minutes) for x% of halogen absorption at 25° in acetic acid, unless otherwise shown:

M/80-$CHPh{:}CPh{\cdot}CO_2H$ + M/80-Cl_2, $x = 50$, $t = 226$. M/40-$CHPh{:}CPh{\cdot}CO_2H$ + M/40-Br_2; + M/40-NaOAc, $x = 20$, $t = 8330$; + M/10-LiCl, $x = 20$, $t = 2380$; + M/10-LiBr, $x = 20$, $t = 5560$. M/80 $CHPh{:}CMe{\cdot}CO_2H$ + M/80-Cl_2, $x = 50$, $t = 26·5$. M/40-$CHPh{:}CMe{\cdot}CO_2H$ + M/40-Br_2: + M/40-NaOAc,

$s = 50$, $t = 1995$; + M/10-LiCl, $s = 50$, $t = 714$; + M/10-LiBr, $s = 50$, $t = 1482$. M/40-CHMe:CH·CO_2H + M/40-Br_2: + M/40-NaOAc, $s = 20$, $t = 420$; + M/10-LiCl, $s = 20$, $t = 114$; + M/10-LiBr, $s = 20$, $t = 145$. M/40-CHMe:CH·CO_2H + M/40-Br_2 in HOAc: + 25% of H_2O, $s = 50$, $t = 54$; + M/5-H_2SO_4, $s = 50$, $t = 64$. M/40-CHEt:CH·CO_2H + M/40-Br_2 in HOAc: + 25% of H_2O, $s = 50$, $t = 36{\cdot}3$; + M/5-H_2SO_4, $s = 50$, $t = 43{\cdot}5$. M/40-CHMe:CMe·CO_2H + M/40-Cl_2, $s = 50$, $t = 1{\cdot}1$. M/40-CHMe:CMe·CO_2H + M/40-Br_2: + M/40-NaOAc, $s = 50$, $t = 220$; + M/10-LiCl, $s = 50$, $t = 66$; + M/10-LiBr, $s = 50$, $t = 197$. M/40-CH_2:CMe·CO_2Me: + M/40-Br_2 + M/5-HBr, $s = 50$, $t = 234$; + M/40-Cl_2, $s = 50$, $t = 11{\cdot}7$. M/40-CHMe:CH·CO_2Me + M/40-Br_2 + M/5-HBr, $s = 20$, $t = 125$. M/40-*cyclo*Hexylideneacetic acid + M/40-Br_2, $s = 50$, $t = 30{\cdot}5$. M/40-*cyclo*Pentylideneacetic acid + M/40-Br_2, $s = 50$, $t = 28{\cdot}8$. M/40-α-Bromocinnamic acid + M/40-Cl_2, $s = 20$, $t = 1300$. M/40-β-Bromocinnamic acid, + M/40-Cl_2, $s = 20$, $t = 46$. M/80-*o*-Chlorocinnamic acid + M/80-Cl_2, $s = 20$, $t = 73$; M/40-*o*-chlorocinnamic acid + M/40-Br_2: + M/40-NaOAc, $s = 20$, $t = 2450$; + M/10-LiBr, $s = 10$, $t = 715$. M/80-*p*-Chlorocinnamic acid + M/80-Cl_2, $s = 20$, $t = 73$; M/40-*p*-chlorocinnamic acid + M/40-Br_2: + M/40-NaOAc, $s = 20$, $t = 275$; + M/10-LiBr, $s = 20$, $t = 223$. M/80-Cinnamylidenemalonic acid + M/80-Br_2 + M/80-NaOAc, $s = 10$, $t = 47{\cdot}5$. M/80-Cinnamylidenemalonic acid + M/80-Br_2 + M/40-HBr, $s = 20$, $t = 0{\cdot}45$. M/80-Cinnamylideneacetic acid + M/80-Br_2 + M/80-NaOAc, $s = 20$, $t = 0{\cdot}09$.

We are indebted to Dr. E. Schwenk, Schering Corporation, New Jersey, U.S.A., for a gift of *cyclo*pentylideneacetic and *cyclo*hexylideneacetic acids.

VICTORIA UNIVERSITY COLLEGE, WELLINGTON, N.Z. [*Received, March 16th*, 1950.]

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337. *The Kinetics of Halogen Addition. Part XVII. Acetylenic Compounds.*

By F. W. ROBERTSON, W. E. DASENT, R. M. MILBURN, and W. H. OLIVER.

Rates of electrophilic halogen addition have been measured for stearolic acid, undecenolic acid, phenylacetylene, tolan, ethyl propylpropiolate, and 1-benzoyl-2-*o*-chlorophenylacetylene, and compared with those of the corresponding ethylenic compounds. The rate-ratio for ethylene to acetylene is increased by electron-repelling groups in the molecule, and reduced by electron-attracting groups, and in the above series varies from 50,000 to 23. A compound such as Cl·C_6H_4·C≡C·COPh, containing a $-T,-I$ group, adds bromine by the nucleophilic mechanism, and the reaction is acid-catalysed in acetic acid solution.

IN the course of the present series of investigations, various acetylenic compounds have been examined and sufficient material appears now to have accumulated to give a preliminary survey of this part of the work. There are certain differences between the acetylenic and ethylenic compounds that may help to elucidate the mechanism of halogen addition. The nature of this relatively complicated two-phase process is still imperfectly understood, in contrast with certain one-phase reactions such as nucleophilic substitution.

An acetylenic group has a greater electron-attractive power than an ethylenic group. For example, whereas phenylethylene has zero dipole moment, the value for phenylacetylene is 0·8 D. Reference to the related nitro-compounds ($PhNO_2$ 3·9, *p*-NO_2·C_6H_4·C≡CH 3·6, *p*-NO_2·C_6H_4·CH_3 4·4 D.) reveals that this moment acts in opposite directions in ethynyl and the electron-repelling methyl. This effect determines some of the chemical characteristics of acetylenic compounds, *i.e.*, their power of salt formation, the *meta*-nitration of phenylpropiolic acid, and the alkali fission of the compound CH≡C·CHO, where the CH≡C group behaves like the CCl_3 group. One such reaction that has been kinetically investigated is the rearrangement of the compounds CHMe:CH·CH(OH)·C≡CH and CHMe:CH·CH(OH)·CH:CH_2 (Braude and Jones, *J.*, 1946, 128), the former reacting less rapidly than the latter by a factor of 3000. This reaction requires electron-accession at the reacting centre, namely the OH group, and is therefore retarded by the electron-attracting ethynyl group.

As electrophilic halogen addition requires electron-accession at the carbon atom which is attacked, it might be expected that acetylenes would be more reactive than the related ethylenes. But this is by no means the case. Some other more powerful effect must therefore operate to control the velocity of halogen addition to unsaturated compounds, and such a factor is related to the polarisability of the double and the triple bond. The position of the bands in the far ultra-violet spectra gives a measure of the relative energy required to shift an electron from the multiple linkage, and the ionisation potential is greater for acetylene than for ethylene (cf. Walsh, *Ann. Reports*, 1947, **44**, 35). The electrons in the π-bond of acetylene are held more tightly than those in the π-bond of ethylene, so that in the former case the electrons are less readily disengaged from their bonding orbitals to link with an approaching halogen

molecule. It is found further that the reduction of ionisation potential is smaller in passing from acetylene to methylacetylene than from ethylene to propylene. That is, the π-electrons in an ethylene are rendered more mobile by a $+I,+T$ group than in an acetylene, and reversibly it might be expected that a $-I,-T$ group in an ethylene might immobilise the electrons relatively more than in the corresponding acetylenic compound. If this is so, the difference in reactivity between ethylenes and acetylenes, for electrophilic halogen addition, should increase with electron-contributing groups and decrease with electron-withdrawing groups. The relative rates (at 25°) of the compounds named in the Table are in accord with this expectation. As the rates for the first four pairs of compounds, owing to widely varying reactivities, were measured at different concentrations, they are recalculated for the concentration M/1000 for the purposes of comparison. This assessment is made on the assumption that these reactions are similar to the previously examined bromine additions with mixed second- and third-order kinetics, and does not involve modification by a factor greater than two. The rates of bromine addition to the last two pairs of compounds are very slow in acetic acid solution and addition would be accompanied by nucleophilic reactions; measurements with these compounds were made under conditions which ensure that the comparison is for electrophilic halogen addition. The velocities shown in the Table and those subsequently quoted are second-order rate coefficients, k_2 (min.$^{-1}$ g.-mol.$^{-1}$ l.).

	Ethylenic compound.	Acetylenic compound.	Rate-ratio.
k_2, Br_2 (HOAc)	Oleic acid, $\sim 3 \times 10^4$	Stearolic acid, 0·65	50,000
k_2, Br_2 (HOAc)	Undecenoic acid, $1{\cdot}2 \times 10^3$	Undecenolic acid, 0·13	9,000
k_2, Br_2 (HOAc)	Styrene, $\sim 7 \times 10^3$	Phenylacetylene, 2·3	3,000
k_2, Br_2 (HOAc)	Stilbene, 11	Tolan, 0·043	250
k_2, Br_2 (HOAc, 50% H_2O)	Methyl α-ethylacrylate, 3·6	Methyl ethylpropiolate, 0·035	100
k_2, Cl_2 (HOAc–NaOAc) ...	1-Benzoyl-2-o-chlorophenyl-ethylene, 1·6	1-Benzoyl-2-o-chlorophenyl-acetylene, 0·079	23

The rate given for oleic acid is that measured for methyl oleate, the substituent at the great distance from the ethylenic link being unlikely to cause any difference. Elaidic acid (*trans*) should have been preferably selected instead of oleic acid, as the other compounds in the list are *trans*-isomers. This would involve a reduction in rate by a factor of between two or three, giving a "rate ratio" of ~20,000. The value for undecenoic acid is in good agreement with the value for α-butylethylene, $k_2 = 1{\cdot}1 \times 10^3$. The rate for ethyl propiolate is as previously measured, and for methyl α-ethylacrylate is that of methyl crotonate multiplied by a factor of 1·8, the ratio of the two acids (*cf. J.*, 1945, 131; and preceding paper).

As shown in the Table, the ratio for related pairs of compound increases with the rates. Sufficient examples have not yet been collected to examine the relation between rate-ratio and constitution for the more slowly reacting compounds. There is the possibility, however, that when two electron-attracting groups are present the acetylene may add halogen more rapidly than the ethylene.

Phenylpropiolic and o-nitrophenylpropiolic acids have also been investigated, but the results for these substances are complicated by their ionisation in acetic acid. This is especially the case for acetylenedicarboxylic acid, which has an acid-strength comparable with that of sulphuric acid. The velocity of bromine addition to the unsaturated anion of this compound was determined, and the following comparison made for the sodium salts in water at 25°, in the presence of sodium acetate to combine with the liberated hydrogen bromide, using as reagent 0·01M-bromine, with 0·015M-potassium bromide. It is apparent that the difference in reactivity observed between acetylene and ethylene molecules persists in the unsaturated anions.

k_2	Fumarate ion, 200	Acetylenedicarboxylate ion, 2

Acetylenic compounds containing $-I,-T$ groups add bromine by a nucleophilic mechanism, which has the general characteristics already observed for the corresponding reactions of ethylenic compounds. This may be illustrated by reference to the rates of bromine addition to 1-benzoyl-2-o-chlorophenylacetylene (M/80-reactants in acetic acid at 25°):

	M/40-NaOAc.	M/40-NaOAc + M/10-LiCl.	M/40-NaOAc + M/10-LiBr.	M/20-H_2SO_4.
k_2	0·0021	0·011	0·024	1·5

The considerable catalysis by lithium chloride and bromide, and the superiority of lithium bromide as a catalyst are indicative of the nucleophilic mechanism (cf. *J.*, 1949, 298), and the high rate in the presence of sulphuric acid shows that the acetylenic compound, like ethylenic compounds of this type (cf. *J.*, 1948, 982), adds bromine by an acid-catalysed nucleophilic reaction. Reference to the rate of chlorine addition ($k_2 = 0{\cdot}079$) shows that the bromine rate

is lower by a factor of 35, the value being ~300 when both compounds react by the electrophilic mechanism. This relatively low rate of chlorine addition explains the difficulty in isolating the dichloro-addition product (Bickel, *J. Amer. Chem. Soc.*, **1948**, **70**, 763), whereas bromine addition was found to take place readily, probably owing to the presence in the bromine of a trace of hydrogen bromide, which would cause a rapid nucleophilic reaction.

(*Added, May 5th, 1950.*) The expectation that an acetylene with two electron-attracting groups might add halogen by the electrophilic mechanism more rapidly than does the corresponding ethylene has been realised. Experiments by W. H. Oliver have shown that ethyl acetylenedicarboxylate (I) adds chlorine more rapidly than ethyl fumarate (II) by a factor of 60, the rates in acetic acid at 25° being for (I) $k_2 = 0{\cdot}0060$ and for (II) $k_2 = 0{\cdot}0001$. Measurements with ethyl maleate indicate that there was considerable *cis-trans* inversion on addition, but its rate should be about three times that of its *trans*-stereoisomer. That the relative reactivity becomes reversed for the ions of the corresponding acids is in accord with expectation, as CO_2^- repels electrons and should therefore make the π-electrons of an ethylene bond more mobile than the corresponding ethylene ion. P. W. R.

Experimental.

All the reactions were measured in acetic acid at 25°, with the technique previously described. The following compounds were used in this investigation: *o*-chlorobenzylideneacetophenone, m. p. 51·5°; 1-benzoyl-2-*o*-chlorophenylacetylene, m. p. 94°, prepared by the method of Bickel (*J. Amer. Chem. Soc.*, **1946**, **68**, 866; **1947**, **69**, 74); phenylacetylene, Eastman Kodak Co., b. p. 143°/760 mm.; tolan (prepared from stilbene), m. p. 61°; acetylenedicarboxylic acid (prepared from fumaric acid), m. p. 175—177° (decomp.); stearolic acid (prepared from methyl oleate), m. p. 46·5° (Found: equiv., 280. Calc.: equiv., 280); undecenolic acid, m. p. 41·5° (Found: equiv., 182. Calc.: equiv., 182); undecenoic acid, fraction b. p. 112—118°/1 mm., recrystallised from light petroleum, m. p. 24·0°; methyl oleate (Found: equiv., 295; I value, 85. Calc.: equiv., 296; I value, 86).

Herewith are details of a typical rate determination:

M/80-*o*-Cl·C_6H_4·C≡C·COPh + M/80-Br_2 + M/40-NaOAc + M/10-LiBr

in HOAc at 25°; 1-ml. samples titrated with M/80-$Na_2S_2O_3$.

Time (mins.)	0	520	1510	2500;	0	970	1950	3000
Titre (ml.)	2·02	1·71	1·40	1·16;	2·01	1·56	1·27	1·06

From the combined % change–time curve the following second-order coefficients were obtained:

x	10	20	30	40	50	
k_2	0·025	0·025	0·025	0·024	0·023	

Herewith are details for M/80-*o*-Cl·C_6H_4·C≡C·COPh + M/80-Br_2 + M/20-H_2SO_4:

Time (mins.)	0	8	25	50;	0	15	30	40
Titre (ml.)	1·99	1·79	1·21	0·64;	2·01	1·55	1·06	0·84

From the combined curve we obtained second-order coefficients showing autocatalysis:

x	10	20	30	40	50	60	
k_2	1·2	1·5	1·7	2·0	2·4	2·9	

The following are additional results for this compound, expressed as times (minutes) for x% halogen absorption at 25° in acetic acid: M/80-*o*-Cl·C_6H_4·C≡C·COPh + M/80-Cl_2 + M/40-NaOAc, $x = 20$, $t = 252$; + M/80-Br_2 + M/40-NaOAc, $x = 10$, $t = 4200$; + M/80-Br_2 + M/10-LiCl, $x = 20$, $t = 1780$. M/80-*o*-Cl·C_6H_4·CH:CH·COPh + M/80-Cl_2 + M/80-NaOAc, $x = 20$, $t = 11{\cdot}0$.

Herewith are the third-order rate coefficients for M/80-tolan + M/80-Br_2 in acetic acid at 25°:

x (% Br_2 absorption)	10	20	30	40	50
k_3	8·2	7·5	7·7	8·0	7·7

Details for this compound (M/80-reactants) are: $x = 20$, $t = 240$; +M/20-LiCl, $t = 120$. For phenylacetylene, $x = 20$, $t = 6{\cdot}0$; +M/20-LiCl, $x = 20$, $t = 3{\cdot}3$. These measurements with lithium chloride show that its catalytic effect is very similar to that for ethylenic compounds that give the normal electrophilic reaction (cf. Table I, *J.*, 1949, 295).

M/1000-Methyl oleate + ½M/1000-Br_2, $x = 50$, $t = 0{\cdot}03$. M/1000-Undecenoic acid + M/1000-Br_2, $x = 50$, $t = 0{\cdot}91$. M/80-Stearolic acid + M/80-Br_2, $x = 20$, $t = 15$. M/80-Undecenolic acid + M/80-Br_2, $x = 20$, $t = 80$.

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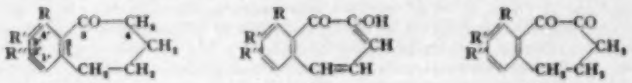
338. *Purpurogallin. Part III. Synthesis of Purpurogallin and Some Analogues.*

By David Caunt, Wilfrid D. Crow, Robert D. Haworth, and Charles A. Vodoz.

2′ : 3′-Dimethoxybenz*cyclo*hepten-3-one (I; R = H, R′ = R″ = OMe) has been oxidised by selenium dioxide to the corresponding 3 : 4-dione (III; R = H, R′ = R″ = OMe), and this oily product has been converted into 4-hydroxy-2′ : 3′-dimethoxybenz*cyclo*heptatrien-3-one (II; R = H, R′ = R″ = OMe) by dehydrogenation with palladium–charcoal in boiling trichlorobenzene. After this preliminary experiment 2′ : 3′ : 4′-trimethoxybenz*cyclo*hepten-3-one (I; R = R′ = R″ = OMe) was converted *via* the oily 3 : 4-dione (III; R = R′ = R″ = OMe) into purpurogallin 2′ : 3′-dimethyl ether (II, R = OH, R′ = R″ = OMe), which was methylated to give the 2′ : 3′ : 4-trimethyl and 2′ : 3′ : 4′ : 4-tetramethyl ethers. Demethylation of the 2′ : 3′ : 4-trimethyl ether yielded purpurogallin (II; R = R′ = R″ = OH) and the 2′-monomethyl ether (II; R = R′ = OH, R″ = OMe). A preliminary summary of these results has already been published (*Chem. and Ind.*, 1949, 149).

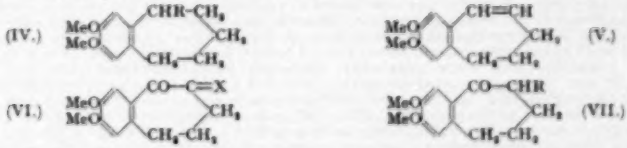
The preparation of 2′ : 3′ : 4′-trimethoxybenz*cyclo*hepten-3-one (I; R = R′ = R″ = OMe) was described in Part I (*J.*, 1948, 1050) but attempts to employ this compound in a synthesis of purpurogallin (II; R = R′ = R″ = OH) were unsuccessful. The cyclic trimethoxy-ketone was oxidised with selenium dioxide, and the oily product probably contained the dione (III; R = R′ = R″ = OMe) because oxidation with hydrogen peroxide yielded γ-(2-carboxy-3 : 4 : 5-trimethoxyphenyl)butyric acid. Attempts to dehydrogenate the crude dione to purpurogallin 2′ : 3′ : 4′-trimethyl ether (II; R = R′ = R″ = OMe) with selenium on palladium–charcoal failed at that time. During these early experiments it was shown that bromination of the cyclic



(I.) (II.) (III.)

monoketone (I; R = R′ = R″ = OMe) with pyridine hydrobromide perbromide yielded 1′-bromo-2′ : 3′ : 4′-trimethoxybenz*cyclo*hepten-3-one, and condensation with ethyl oxalate in the presence of potassium ethoxide gave ethyl 3-keto-2′ : 3′ : 4′-trimethoxybenz*cyclo*heptene-4-glyoxylate, but the preparation of the cyclic trimethoxy-ketone (I; R = R′ = R″ = OMe) was tedious, and it was decided to make a detailed examination of the properties of the more accessible dimethoxy-analogue (I; R = H, R′ = R″ = OMe).

The preparation of β-(3 : 4-dimethoxyphenyl)valeric acid (Haworth and Atkinson, *J.*, 1938, 808) has been simplified by an improved preparation of glutaric acid. Cyclisation of the valeric acid with phosphoric oxide in benzene, or preferably by the successive actions of phosphorus pentachloride and stannic chloride in this solvent, gave good yields of 2′ : 3′-dimethoxybenz*cyclo*hepten-3-one. This highly crystalline ketone gave a semicarbazone, a 2 : 4-dinitrophenylhydrazone, and an oxime, and reduction of the last with sodium amalgam yielded 3-amino-2′ : 3′-dimethoxybenz*cyclo*heptene (IV; R = NH_2), m. p. 55°. Attempts to convert this base into



(IV.) (V.) (VI.) (VII.)

the corresponding 3-dimethylamino-derivative by refluxing it with methyl iodide and sodium carbonate in acetone solution resulted in deamination with the formation of 2′ : 3′-dimethoxybenz*cyclo*hepta-1 : 3-diene (V); in methyl alcohol a trimethoxy-derivative, probably 2′ : 3′ : 3-trimethoxybenz*cyclo*heptene (IV; R = OMe), resulted. 2′ : 3′-Dimethoxybenz*cyclo*hepten-3-one (I; R = H, R′ = R″ = OMe) reacted with ethyl formate in benzene in the presence of sodium methoxide, yielding 2′ : 3′-dimethoxy-4-hydroxymethylenebenz*cyclo*hepten-3-one (VI; X = CH·OH), and with amyl nitrite in methanolic hydrogen chloride yielding 4-oximino-2′ : 3′-dimethoxybenz*cyclo*hepten-3-one (VI; X = N·OH). Attempts to hydrolyse the oximino-derivative to the corresponding 3 : 4-dione (III; R = H, R′ = R″ = OMe) gave unsatisfactory

results (see p. 1634), and reduction with zinc and acetic acid (Hoffmann and Lott, *J. Biol. Chem.*, 1948, **172**, 327) gave 2′ : 3′-dimethoxybenz*cyclo*hepten-3-one (I; R = H, R′ = R″ = OMe). The oximino-ketone (VI; X = N·OH) was readily reduced by hydrogen in presence of palladium charcoal in methyl alcohol containing hydrogen chloride to the hydrochloride of 4-amino-2′ : 3′-dimethoxybenz*cyclo*hepten-3-one (VII; R = NH_2). This was decomposed by nitrous acid to an oily product, the *p*-nitrobenzoate, m. p. 182—183°, of which gave analytical figures in agreement with those required for a *p*-nitrobenzoate of 4-hydroxy-2′ : 3′-dimethoxybenz*cyclo*hepten-3-one (VII; R = OH), but further work along these lines did not appear to be very promising.

It was found that 2′ : 3′-dimethoxybenz*cyclo*hepten-3-one (I; R = H, R′ = R″ = OMe) was oxidised by selenium dioxide in boiling ethanol, acetic anhydride, dioxan, or preferably butanol. The resulting pale yellow oily 2′ : 3′-dimethoxybenz*cyclo*heptene-3 : 4-dione (III; R = H, R′ = R″ = OMe) gave a crystalline dinitrophenylhydrazone, but could not be dehydrogenated to 4-hydroxy-2′ : 3′-dimethoxybenz*cyclo*heptatrien-3-one (II; R = H, R′ = R″ = OMe) with palladium black or palladium–charcoal. At this stage Professor J. W. Cook, F.R.S., kindly informed us of the conversion of benz*cyclo*heptene-3 : 4-dione (III; R = R′ = R″ = H) into 4-hydroxybenz*cyclo*heptatrien-3-one (II; R = R′ = R″ = H) (Cook and Somerville, *Nature*, 1949, **163**, 410) by means of palladium-charcoal in boiling trichlorobenzene. After some practice with the reagent, the dimethoxy-dione was converted in 9% yield into 4-hydroxy-2′ : 3′-dimethoxybenz*cyclo*heptatrien-3-one (II; R = H, R′ = R″ = OMe), m. p. 147°, which was soluble in alkali, gave a red ferric test, and a crimson coupling product with diazotised *p*-toluidine.

After this experience, renewed attempts were made to convert 2′ : 3′ : 4′-trimethoxybenz*cyclo*hepten-3-one (I; R = R′ = R″ = OMe) into purpurogallin (II; R = R′ = R″ = OH). The benz*cyclo*heptenone was oxidised by selenium dioxide in boiling butanol to the dione (III; R = R′ = R″ = OMe) (2 : 4-dinitrophenylhydrazone, m. p. 181°). Dehydrogenation was then effected with a palladium–charcoal catalyst in boiling trichlorobenzene, and acidification of the alkali-soluble products yielded purpurogallin 2′ : 3′-dimethyl ether (II; R = OH, R′ = R″ = OMe), identical with the dimethyl ether, m. p. 156°, described in Part I (p. 1049). Obviously this synthesis of the dimethyl ether proves that the tropolone-hydroxyl group is not methylated, and this together with the ready acid hydrolysis of the 4′-methyl ether group of purpurogallin 2′ : 3′ : 4′ : 4-tetramethyl ether to the 2′ : 3′ : 4-trimethyl ether (see Part I, p. 1049; Part II, *J.*, 1949, 3271, footnote) constitute powerful evidence for the structure of the purpurogallin 2′ : 3′-dimethyl ether. This 2′ : 3′-dimethyl ether was converted by diazomethane into purpurogallin 2′ : 3′ : 4-trimethyl ether, identical with the product described in Part I, and demethylation of this with hydrogen bromide gave purpurogallin (II; R = R′ = R″ = OH), m. p. 276°, together with a small amount of purpurogallin 2′-methyl ether, m. p. 193°. This monomethyl ether was first obtained by Willstätter and Heiss (*Annalen*, 1923, **433**, 17), who regarded it as purpurogallin 4-methyl ether; the new structure has been proved by unpublished results obtained by Mr. A. Critchlow which will be reported shortly.

Experimental.

Glutaric Anhydride.—Difficulty was experienced in reaching the yields quoted (*Org. Synth.*, **10**, 58) for ethyl propane-1 : 1 : 3 : 3-tetracarboxylate. However a considerable improvement was effected by heating the high boiling residual ethyl pentane-1 : 1 : 3 : 3 : 5 : 5-hexacarboxylate (450 g.) with sodium (20·5 g.) in ethyl alcohol (270 c.c.) at 110—115° for 8 hours; decomposition with ice and hydrochloric acid and extraction with ether gave ethyl propane-1 : 1 : 3 : 3-tetracarboxylate (165 g.), b. p. 215—225°/28 mm., unchanged pentanehexacarboxylate (153 g.), and ethyl methylenemalonate (30 g.). Even with this improvement the total yield (60%) was inferior to that obtained by the following modification of Welch's method (*J.*, 1931, 673). Alcoholic potassium hydroxide (5 c.c.; 10%) was added to ethyl malonate (400 g.) and paraformaldehyde (33·5 g.), and the mixture was heated on the water-bath. Further additions of 10% alcoholic potassium hydroxide were made (0·2 and 0·3 c.c. after 1 and 5 hours respectively). After a total of 6 hours' heating, the catalyst was destroyed by neutralisation with hydrochloric acid, and the product distilled as described in *Org. Synth.*, *loc. cit.*; ethyl malonate (110 g.) was recovered, and ethyl propane-1 : 1 : 3 : 3-tetracarboxylate (275 g.) was obtained, together with a small residue (12 g.).

The hydrolysis of the propanetetracarboxylate to glutaric acid was carried out as described (*loc. cit.*), and the conversion into glutaric anhydride was achieved with acetyl chloride in the usual way.

γ-(3 : 4-Dimethoxybenzoyl)butyric Acid and δ-(3 : 4-Dimethoxyphenyl)valeric Acid.—A cooled solution of veratrole (6 g.) and glutaric anhydride (5 g.) in nitrobenzene (20 c.c.) was gradually added at 5° to a solution of aluminium chloride (12 g.) in nitrobenzene (40 c.c.). After 3 hours at 0°, the mixture was decomposed by shaking it with ice and dilute hydrochloric acid for 2 hours, and the precipitated keto-acid was collected (4·8 g.). The nitrobenzene was separated from the filtrate, washed with water, and extracted with sodium carbonate solution, and the acid (1·2 g.) recovered. The combined acids, recrystal-

lised from hot water or chloroform–light petroleum (b. p. 40—60°), gave γ-3 : 4-dimethoxybenzoylbutyric acid, m. p. 140—145° (Haworth and Atkinson, *loc. cit.*, give m. p. 140—142°); the *methyl* ester, b. p. 195—198°, separated from chloroform–light petroleum (b. p. 60—80°) in colourless needles, m. p. 58—59° (Found: C, 63·0; H, 6·5. $C_{16}H_{18}O_5$ requires C, 63·1; H, 6·8%). The constitution of the keto-acid was established by oxidation with potassium permanganate (4 parts) in dilute sodium hydrogen carbonate solution at 40°; veratric acid, m. p. 180°, was isolated.

δ-(3 : 4-*Dimethoxyphenyl*)*valeric acid*, b. p. 193—195°/0·01 mm., m. p. 72°, was prepared by Clemmensen reduction of the above keto-acid as described by Haworth and Atkinson, but the addition of toluene (1 volume for 1 part of keto-acid) was advantageous.

2′ : 3′-*Dimethoxybenzo*cyclo*hepten*-3-*one* (I; R = H, R′ = R″ = OMe).—(*a*) A solution of δ-(3 : 4-dimethoxyphenyl)valeric acid (1 g.) in benzene (50 c.c.) was refluxed with phosphoric oxide (10 g.) for 10 minutes. After decomposition with water, the benzene layer was washed with dilute aqueous sodium hydroxide and dried, the solvent removed, and the residue distilled at 0·01 mm., the yield being 0·5 g.

(*b*) Phosphorus pentachloride (11 g.) was added to a solution of δ-3 : 4-dimethoxyphenylvaleric acid (11·8 g.) in dry benzene (50 c.c.) at 0°. After 30 minutes at 0° and then 30 minutes at room temperature, the mixture was gently heated on the water-bath for 15 minutes and then cooled to 0°, and stannic chloride (13·9 g.) in benzene (450 c.c.) added. After 2 hours at 0°, the dark complex was decomposed with ice (200 g.) and concentrated hydrochloric acid (30 c.c.), and the organic layer was washed successively with dilute hydrochloric acid, sodium hydroxide solution, and water. The solvent was removed and the residue distilled at 0·01 mm. the yield being 8·7 g.

2′ : 3′-*Dimethoxybenzo*cyclo*hepten*-3-*one* (I; R = H, R′ = R″ = OMe).—This *ketone* had b. p. 161°/0·01 mm. and crystallised from aqueous methyl alcohol or ether–light petroleum (b. p. 60—80°) in colourless prisms, m. p. 63—64° (Found: C, 71·1; H, 7·3. $C_{13}H_{16}O_3$ requires C, 71·1; H, 7·3%). The *oxime* crystallised from ethyl alcohol in colourless prisms, m. p. 152° (Found: C, 66·0; H, 7·4. $C_{13}H_{17}O_3N$ requires C, 66·3; H, 7·3%); the *semicarbazone* separated from aqueous methyl alcohol in colourless needles, m. p. 190—192° (Found: C, 60·8; H, 6·8. $C_{14}H_{19}O_3N_3$ requires C, 60·6; H, 6·9%), and the 2 : 4-*dinitrophenylhydrazone* from chloroform–methyl alcohol in orange prisms, m. p. 234—236° (Found: C, 57·0; H, 4·9; N, 14·0. $C_{19}H_{18}O_6N_4$ requires C, 57·0; H, 5·0; N, 14·0%).

2′ : 3′-*Dimethoxy*-4-*hydroxymethylenebenzo*cyclo*hepten*-3-*one* (VI; X = CH·OH).—The foregoing ketone (1 g.) in benzene (8 c.c.) was added to a suspension of sodium methoxide (from 0·4 g. of sodium) in a mixture of benzene (7 c.c.) and ethyl formate (0·68 g.). After 12 hours' shaking at room temperature, the mixture was decomposed with ice, and the product, isolated by means of sodium hydroxide and recovered, was taken up in chloroform. Removal of the solvent gave the *hydroxymethylene-ketone* which crystallised from benzene–light petroleum (b. p. 60—80°) in colourless needles (0·88 g.), m. p. 135—136° (Found: C, 67·9; H, 6·6. $C_{14}H_{16}O_4$ requires C, 67·6; H, 6·5%), which gave a brownish-violet ferric test.

3-*Amino*-2′ : 3′-*dimethoxybenzo*cyclo*heptene* (IV; R = NH_2).—3-Oximino-2′ : 3′-dimethoxybenzocycloheptene (1·2 g.), m. p. 152°, in 50% aqueous methyl alcohol (25 c.c.) was reduced at 50° by the gradual addition of 4% sodium amalgam (40 g.). The mixture was stirred, glacial acetic acid was added periodically to maintain slight acidity, and, when the amalgam was exhausted, hydrochloric acid was added until the mixture was acid to Congo-red. The methyl alcohol was removed under reduced pressure, neutral impurities were removed in ether, and after basification the 3-*amino*-compound was isolated with ether; it had b. p. 120°/0·2 mm. and solidified to a mass of colourless prisms, which after crystallisation from ether–light petroleum (b. p. 40—60°) had m. p. 54—55° (Found: C, 70·7; H, 8·3; N, 6·1. $C_{13}H_{19}O_2N$ requires C, 70·6; H, 8·6; H, 6·3%). The *hydrochloride*, prepared in ether, crystallised from methyl alcohol–ether in colourless prisms, m. p. 234° (Found: C, 60·7; H, 7·9; N, 5·6. $C_{13}H_{20}O_2NCl$ requires C, 60·6; H, 7·8; N, 5·4%). The *acetyl* derivative, prepared with acetic anhydride, crystallised from ethyl alcohol in colourless needles, m. p. 166° (Found: C, 68·5; H, 8·3. $C_{15}H_{21}O_3N$ requires C, 68·4; H, 8·0%).

2′ : 3′-*Dimethoxybenzo*cyclo*hepta*-1 : 3-*diene* (V).—The base (IV; R = NH_2) (3·8 g.) was warmed in acetone (10 c.c.) with methyl iodide (11·0 g.) and anhydrous sodium carbonate (7 g.) for 1 hour. After evaporation to dryness, extraction with ether gave 2′ : 3′-*dimethoxybenzocyclohepta*-1 : 3-*diene* as a pale yellow oil (1·0 g.), b. p. 150°/0·2 mm. (Found: C, 76·2; H, 7·7; OMe, 29·5. $C_{13}H_{14}O_2$ requires C, 76·4; H, 7·0; OMe, 30·4%).

2′ : 3′ : 3-*Trimethoxybenzo*cyclo*heptene* (IV; R = OMe).—The base (IV; R = NH_2) (6·0 g.), methyl iodide (17·5 g.), and anhydrous sodium carbonate were refluxed for 1 hour with methanol (10 c.c.). Evaporation and extraction with ether yielded 2′ : 3′ : 3-*trimethoxybenzocycloheptene* which separated from methyl alcohol in large prisms (2·3 g.), m. p. 62° (Found: C, 71·1; H, 8·6; OMe, 39·7. $C_{14}H_{20}O_3$ requires C, 71·2; H, 8·5; OMe, 39·4%).

4-*Oximino*-2′ : 3′-*dimethoxybenzo*cyclo*hepten*-3-*one* (VI; X = N·OH).—2′ : 3′-Dimethoxybenzocycloheptene-3-one (2·5 g.) and redistilled amyl nitrite (1·8 c.c.) in methyl alcohol (5 c.c.) were saturated with hydrogen chloride at −13°. After 7 hours at −8°, the red product was collected and, digested at 30° with 30% aqueous methyl alcohol, and the yellow *oximino*-derivative (1·2 g.) collected and crystallised from methyl alcohol; yellow prisms, m. p. 178° (Found: C, 62·5; H, 5·9; N, 5·6. $C_{13}H_{15}O_3N$ requires C, 62·6; H, 6·1; N, 5·6%), were obtained, which dissolved in sodium hydroxide solution and gave a negative test with cobalt nitrate.

4-*Amino*-2′ : 3′-*dimethoxybenzo*cyclo*hepten*-3-*one* (VII; R = NH_2).—The 4-oximino-derivative (VI; X = N·OH) (4·5 g.) was reduced in methyl alcohol (45 c.c.) containing some hydrogen chloride in presence of 10% palladised charcoal (0·5 g.). After 7 hours, when absorption of hydrogen ceased, chloroform was added to redissolve the hydrochloride which had gradually separated, the catalyst was removed, the filtrate was concentrated and cooled, and the 4-*amino*-2′ : 3′-*dimethoxybenzocyclohepten*-3-*one hydrochloride* (4·0 g.) collected; crystallisation from methyl alcohol–ether gave colourless needles, m. p. 255° (Found: C, 57·6; H, 6·8. $C_{13}H_{18}O_3NCl$ requires C, 57·3; H, 6·7%). A solution of this hydrochloride (0·5 g.) and sodium nitrite (0·13 g.) in water (7 c.c.) was warmed at 60°. Nitrogen (35 c.c. at 22°/748 mm.) was evolved and the red oil which separated was taken up in chloroform and recovered. This

nitrogen-free oil (0·43 g.) was mixed with benzene (5 c.c.), *p*-nitrobenzoyl chloride (0·4 g.), and pyridine (12 c.c.) and heated on the water-bath for 3 hours. The *p-nitrobenzoate* of 4-*hydroxy*-2′ : 3′-*dimethoxybenzo*cyclo*hepten*-3-*one* (VII; R = OH) separated and crystallised from benzene in colourless prisms, m. p. 182—183° (Found: C, 62·1; H, 5·1. $C_{26}H_{21}O_7N$ requires C, 62·3; H, 5·0%).

2′ : 3′-*Dimethoxybenzo*cyclo*heptane*-3 : 4-*dione* (III; R = H, R′ = R″ = OMe).—2′ : 3′-Dimethoxybenzo*cyclo*hepten-3-one (I; R = H, R′ = R″ = OMe) (5·8 g.), was refluxed in *n*-butyl alcohol (60 c.c.) for 3 hours with selenium dioxide (3·0 g.). The filtered solution was evaporated under reduced pressure, and the residue was taken up in ether and distilled. 2′ : 3′-Dimethoxybenzo*cyclo*hepten-3-one (1·8 g.), b. p. 159—163°/0·1 mm., was recovered, and the *dione* (III; R = H, R′ = R″ = OMe) was obtained as an orange, very viscous oil (2·2 g.), b. p. 175—180°/0·1 mm. (Found: C, 66·5; H, 6·2. $C_{15}H_{14}O_4$ requires C, 66·7; H, 6·0%); it yielded a 2 : 4-*dinitrophenylhydrazone*, which crystallised from toluene in yellow needles, m. p. 253° (Found: C, 55·4; H, 4·1; N, 13·8. $C_{21}H_{18}O_7N_4$ requires C, 55·1; H, 4·4; N, 13·5%). The dione was also obtained in poor yields as follows: the oximino-derivative (VI; X = N·OH) (13·4 g.), dioxan (70 c.c.), concentrated hydrochloric acid (7 c.c.), and pyruvic acid (5 g.) were refluxed for 40 minutes and gave much ether-insoluble resin. The ethereal extract yielded the dione (0·42 g.) which was characterised by the 2 : 4-dinitrophenylhydrazone, m. p. 253°.

4-*Hydroxy*-2′ : 3′-*dimethoxybenzo*cyclo*heptatrien*-3-*one* (II; R = H, R′ = R″ = OMe).—The dione (III; R = H, R′ = R″ = OMe) (1·5 g.) was refluxed for 10 hours in *s*-trichlorobenzene (8 g.; b. p. 208°) with 10% palladised charcoal (1 g.) in a nitrogen atmosphere. After dilution with benzene, the filtered solution was washed successively with sodium hydrogen carbonate solution and water, and extracted with sodium hydroxide solution. The product (II; R = H, R′ = R″ = OMe), liberated by acidification and isolated with ether, crystallised from *cyclo*hexane in deep-yellow prisms (0·11 g.), m. p. 147° (Found: C, 67·2; H, 5·3. $C_{15}H_{12}O_4$ requires C, 67·2; H, 5·2%), dissolved in concentrated hydrochloric acid to a deep-yellow solution, and gave a blood-red ferric test and a crimson precipitate with diazotised *p*-toluidine.

γ-(3 : 4 : 5-*Trimethoxybenzoyl*)*butyric Acid and* δ-(3 : 4 : 5-*Trimethoxyphenyl*)*valeric Acid*.—The former acid was prepared as described in Part I (*loc. cit.*, p. 1050) but the hydrolysis with 20% sulphuric acid was allowed to proceed for 90 hours. Instead of reducing this keto-acid as described in Part I (*loc. cit.*, p. 1050) it was preferable on a larger scale to reduce it by Clemmensen's method as follows: The keto-acid (23 g.) in toluene (200 c.c.) was gently refluxed for 15 hours with amalgamated zinc (100 g.) and concentrated hydrochloric acid (200 c.c.). δ-(3 : 4 : 5-Trimethoxyphenyl)valeric acid (20·8 g.), m. p. 68°, was obtained from the toluene layer and purified by vacuum-distillation.

2′ : 3′ : 4′-*Trimethoxybenzo*cyclo*hepten*-3-*one* (I; R = R′ = R″ = OMe).—The following conditions proved superior to those described in Part I (*loc. cit.*, p. 1050). δ-(3 : 4 : 5-Trimethoxyphenyl)valeric acid (12·5 g.) in benzene (100 c.c.) was treated with phosphorus pentachloride (9·8 g.) at 0° for ½ hour and the reaction completed by warming the mixture for 10 minutes on the water-bath. The solution was cooled to 0° and gradually added, with shaking, to an ice-cold solution of stannic chloride (12·25 g.) in benzene (2 l.). After 2 hours at 0° the solution was decomposed by the addition of ice (200 g.) and concentrated hydrochloric acid (200 c.c.), and the benzene layer washed successively with dilute hydrochloric acid, dilute sodium hydroxide solution, and water. The cyclic ketone (I; R = R′ = R″ = OMe) was obtained from the benzene layer, and crystallised from *cyclo*hexane in colourless rhombs (7·8 g.), m. p. 102°. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in orange prisms, m. p. 186° (Found: C, 55·8; H, 5·2; N, 13·0. $C_{22}H_{22}O_7N_4$ requires C, 56·0; H, 5·3; N, 13·1%). In Part I the m. p. was recorded as 176—177°. The *semicarbazone* crystallised from methyl alcohol in colourless needles, m. p. 165—166° (Found: C, 58·5; H, 6·9. $C_{18}H_{25}O_4N_3$ requires C, 58·6; H, 6·9%).

1′-*Bromo*-2′ : 3′ : 4′-*trimethoxybenzo*cyclo*hepten*-3-*one* (by P. L. Pauson).—The cyclic ketone (I; R = R′ = R″ = OMe) (0·25 g.) was gently warmed with pyridine hydrobromide perbromide (Dierassi and Scholz, *J. Amer. Chem. Soc.*, 1948, **70**, 417), (0·32 g.) in acetic acid (10 c.c.). The *bromo*-compound, precipitated by addition of water as a brown oil which solidified during several weeks, crystallised from methyl alcohol in colourless needles, m. p. 79° (Found: C, 50·7; H, 5·2. $C_{14}H_{17}O_4Br$ requires C, 51·0; H, 5·2%), which were unaffected when boiled with potassium acetate in acetic acid. Pure products were not obtained during attempted bromination of the ketone with *N*-bromosuccinimide in carbon tetrachloride or with bromine in chloroform.

Ethyl 3-*Keto*-2′ : 3′ : 4′-*trimethoxybenzo*cyclo*heptane*-4-*glyoxylate* [by P. L. Pauson).—2′ : 3′ : 4′-Trimethoxybenzo*cyclo*hepten-3-one (I; R = R′ = R″ = OMe) (0·5 g.) was added to the solution obtained by adding ethyl oxalate (0·7 g.) in ether (5 c.c.) to a suspension of potassium ethoxide, prepared from potassium (0·16 g.) and ethyl alcohol (0·2 g.) in ether (15 c.c.). After 2 hours at room temperature, the mixture was decomposed with ice, the combined aqueous layers were acidified with ice-cold dilute hydrochloric acid, and the product was collected; it crystallised from ethyl alcohol in pale yellow prisms, m. p. 120° (Found: C, 61·6; H, 6·3. $C_{18}H_{22}O_7$ requires C, 61·7; H, 6·3%).

2′ : 3′ : 4′-*Trimethoxybenzo*cyclo*heptene*-3 : 4-*dione* (III; R = R′ = R″ = OMe).—2′ : 3′ : 4′-Trimethoxybenzo*cyclo*hepten-3-one (I; R = R′ = R″ = OMe) (5 g.) was refluxed with *n*-butyl alcohol (60 c.c.) and selenium dioxide (2·3 g.) for 3 hours. After cooling, the mixture was filtered from selenium, the filtrate evaporated under reduced pressure, and the residue taken up in ether. Removal of the ether and distillation of the residue yielded unchanged benzsuberone (I; R = R′ = R″ = OMe) (2·7 g.), b. p. 175—180°/0·2 mm., and the *dione* (III; R = R′ = R″ = OMe) (12·2 g.), a pale yellow oil, b. p. 200—210°/0·2 mm. (Found: C, 63·6; H, 6·3. $C_{18}H_{18}O_5$ requires C, 63·6; H, 6·1%), which gave a *mono*-2 : 4-*dinitrophenylhydrazone* crystallising from ethyl acetate in yellow prisms, m. p. 181° (Found: C, 54·1; H, 4·5; N, 12·6. $C_{24}H_{22}O_8N_4$ requires C, 54·1; H, 4·5; N, 12·6%).

4 : 4′-*Dihydroxy*-2′ : 3′-*dimethoxybenzo*cyclo*heptatrien*-3-*one* (II; R = OH, R′ = R″ = OMe).—The above dione (1 g.) was dehydrogenated in boiling trichlorobenzene as described above for the dimethoxy-analogue, the sodium hydroxide extract was acidified at 50°, and the product isolated with ether. The red solid, crystallised first from *cyclo*hexane and then from methyl alcohol, gave orange plates (0·09 g.), m. p. 156°, identical with purpurogallin dimethyl ether described in Part I (*loc. cit.*, p. 1049). This ether (0·08 g.) in dioxan (5 c.c.) with diazomethane (0·02 g.) in ether (500 c.c.) gave

4′-hydroxy-2′ : 3′ : 4-trimethoxybenzocycloheptatrien-3-one, as yellow prisms (from alcohol), m. p. 176°, identical with purpurogallin trimethyl ether. Further methylation to purpurogallin tetramethyl ether, m. p. 94°, with methyl sulphate and potassium hydroxide was accomplished as described in Part I (*loc. cit.*, p. 1049).

Demethylation of Purpurogallin 2′ : 3′ : 4′-Trimethyl Ether.—The synthetic trimethyl ether (0·06 g.) described above was heated for 1 hour with hydrobromic acid (5 c.c.; *d* 1·48). The solution was evaporated to dryness under reduced pressure and the product, after dissolution in and recovery from dioxan, was sublimed at 0·02 mm. and separated into three fractions characterised by the sublimation bath-temperatures of (*a*) 150—185°, (*b*) 185—210°, and (*c*) 210—290°. Resublimation of fraction (*c*) yielded a fraction (*d*) subliming at 265—285°, which yielded purpurogallin (0·015 g.) as red prisms, m. p. 276°, undepressed on admixture with an authentic specimen, after crystallisation from anisole.

Fraction (*b*), crystallised from chloroform, yielded purpurogallin 2′-monomethyl ether as orange prisms (0·002 g.), m. p. 193°, identical with a sample prepared from pyrogallol and 3-methoxycatechol (Willstatter and Heiss, *loc. cit.*, give m. p. 183°, but this has been raised to 193° by sublimation).

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THE UNIVERSITY, SHEFFIELD, 10. [*Received, March 30th*, 1950.]

NOTES.

The Raman Spectrum of the $[AuCl_4]^-$ *Ion.*

By J. D. S. GOULDEN, ALLAN MACCOLL, and D. J. MILLEN.

A THEORETICAL study of the vibrations of square molecules (Mathieu, *J. Chim. physique*, **1939**, **36**, 271, 308; Maccoll, *J. Proc. Roy. Soc. N.S.W.*, **1944**, **77**, 130) shows that three frequencies should be active in the Raman spectra of $[AX_4]^-$ ions. The modes of vibration are shown in the annexed diagram. Of the lines corresponding to these, the first will be polarised, and the last two depolarised. Further, the ν_1 and ν_3 frequencies will in the first approximation be identical, separation only occurring by virtue of cross terms in the potential function. Mathieu (*loc. cit.*) has examined the Raman spectra of the ions $[Ni(CN)_4]^{--}$, $[Pd(CN)_4]^{--}$, and $[Pt(CN)_4]^{--}$, but it is only for the last two that the spectra are in any way complete. The spectral study confirmed the planar structure of these ions.

Simple examples of square complexes are the ions $[AuCl_4]^-$ and $[ICl_4]^-$. These arise from the electronic configurations dsp^2 and d^2sp^2 respectively, the unshared pairs in the latter compound occupying the remaining two octahedral positions (Pauling, "The Nature of the Chemical Bond," Cornell Univ. Press, New York, 1940).

Since solutions of "gold chloride," $HAuCl_4.4H_2O$ are yellow, it was necessary to employ the Hg_{5461} green line for excitation, as the solution absorbed light of shorter wave-lengths. A saturated aqueous solution of "gold chloride" was introduced into a small horn-shaped Raman tube of 4-c.c. capacity. Light from a single horizontal D.C. mercury arc was used as a source of exciting radiation, and the Hg_{5461} line was isolated by passing the light through a 1-cm. layer of a saturated cupric chloride solution, and through a 1-cm. layer of a saturated neodymium trichloride–praseodymium trichloride solution. The

second filter served to reduce the intensity of the Hg-yellow lines. The spectra were observed using an f4 Hilger spectrograph, the dispersion in the relevant region of the spectrum being about 180 A. per mm. The experimental arrangement of filters, cell, and reflectors has been described elsewhere (Goulden and Millen, *J.*, in the press). Exposures of about four days with a slit width of 0·2 mm. were required to produce a spectrum of suitable intensity. Previously prepared calibration tables were used for determining the frequencies.

A number of exposures were made, but even with the longest exposure only a single Raman frequency, at 370 ± 5 cm.$^{-1}$, appeared. A microphotometer trace showed a double peak at this frequency. Similar exposures with aqueous potassium tetrachloroperiodate solutions showed that this solution absorbed the Hg-green light too strongly to give a Raman spectrum.

The frequency 370 cm.$^{-1}$ of the aurichloride ion can reasonably be identified with the pair of frequencies ν_1, ν_3, which, as has been pointed out previously, will lie very close to one another. This is borne out by Mathieu's experiments with the platinicyanide ion, for which the observed frequencies were 455, 465 cm.$^{-1}$. The third frequency for aurichloride might be expected from Mathieu's results to lie at about 90 cm.$^{-1}$, in which position it would be obscured by the breadth of the exciting line. The observed spectrum of the aurichloride ion thus confirms the square structure.

The stretching force constant may be calculated from the observed frequency by means of

$$\nu_1 = \frac{1}{2\pi c}\left(\frac{k}{m}\right)^{1/2}$$

where k is the force constant of the Au–Cl bond and m is the mass of the chlorine atom (Maccoll, *loc. cit.*), leading to $k = 2{\cdot}66 \times 10^5$ dynes cm.$^{-1}$. This value is of the same order of magnitude as those for the ions $[Pd(CN)_4]^{--}$ and $[Pt(CN)_4]^{--}$ given by Mathieu, *viz.*:

Ion.	(cm.$^{-1}$).	$k \times 10^{-5}$ (dynes cm.$^{-1}$).
$[Pd(CN)_4]^{--}$	439	2·93
$[Pt(CN)_4]^{--}$	465	3·30
$[AuCl_4]^{-}$	370	2·66

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The Determination of Carbohydrate Residues in Pentose Nucleic Acids. By G. R. Barker.

In connection with work directed towards the examination of pentose nucleic acids from various tissues, it was necessary to have available a convenient method for the determination of the pentose nucleic acid content of materials obtained both for purposes of characterisation and as a guide in the extraction procedures. Analytical methods based on the determination either of heterocyclic bases or of phosphorus are inconvenient, because they do not distinguish between the pentose and the deoxypentose nucleic acids or because of their complexity. Colorimetric analysis for pentoses which are first converted into furfuraldehyde (for references see Davidson, *Cold Spring Harb. Symp. quant. Biol.*, 1947, **12**, 50) suffers from disadvantages. First, it is susceptible to interference from various materials not yielding furfuraldehyde and on this account is not applicable directly to crude nucleoproteins (Schneider, *J. Biol. Chem.*, 1945, **161**, 293). Secondly, the techniques so far described are liable to grave error in that only purine-bound pentose and not pyrimidine-bound pentose is normally converted into furfuraldehyde in anything approaching quantitative yield. Thus the apparent quantity of nucleic acid measured is dependent on the ratio of purine to pyrimidine nucleotides in the polynucleotide. It is assumed that this criticism applies also to the more recent method of Dische (*J. Biol. Chem.*, 1949, **181**, 379) since pyrimidine compounds are not discussed by him.

It has now been found that these difficulties are largely overcome by the use of Dunstan and Gillam's method (*J.*, 1949, S140). Since the programme of work in which this method is being used will not be complete for some time and the adaptation of the procedure for use in the nucleotide field has proved highly successful, the applicability of the method to the analysis of materials containing pentose nucleotides, together with necessary modifications in technique, are now briefly reported.

By use of the method as described, 100% recovery of ribose, computed from the spectroscopic measurement of furfuraldehyde, was obtained from adenosine, guanosine, yeast adenylic acid, and guanylic acid. With the pyrimidine nucleosides and nucleotides, although recoveries of ribose were higher than with other techniques, variable results were obtained unless the conditions of the steam-distillation were more rigidly controlled. Thus, for instance, if the rate of distillation was too rapid, the time occupied in collecting a reasonably convenient volume of distillate was insufficient for complete hydrolysis of the pyrimidine compounds which are very resistant to fission by acids: if, on the other hand, distillation was too slow, furfuraldehyde was not removed rapidly enough and underwent some decomposition, with a consequent low recovery. By distillation at a rate of approximately 5 c.c. per minute, maintained by a manostat controlling the burner of the steam generator, and collection of 110 c.c. of distillate, consistent results were obtained (see Table). Under these conditions, which may vary slightly with the dimensions of the apparatus and should be first found by experiment, recoveries of ribose from uridine, cytidine, and cytidylic acid were reproducible within the limits of accuracy of the method as stated by Dunstan and Gillam and were far nearer to the theoretical values than those obtained by other methods, which give results never above 50% of those expected and mostly far less:

Material.	Yield of furfuraldehyde, expressed as % recovery of ribose (mean value).	Material.	Yield of furfuraldehyde, expressed as % recovery of ribose (mean value).
Cytidine	93·9	Cytidylic acid	80·2
Uridine	90·8	Yeast nucleic acid	88·5

Moreover, this method is simpler in operation than that of Massart and Hoste (*Biochim. Biophys. Acta*, 1947, **1**, 83) which is reported (Kerr, Seraidarian and Wargon, *J. Biol. Chem.*, 1949, **181**, 761) to give unreliable results under some conditions.

As a result of controlling the rate of flow of steam, it was found that the necessary distillation temperature was more easily maintained and the method was made semi-automatic in the following ways. First, a mercury thermostat was included in the distillation tube, and secondly, the distillation was stopped mechanically by placing the receiver on the pan of a rough balance which activated a tilting mercury switch controlling the gas supply both to the burner of the steam generator and to that beneath the distillation tube.

By this method it is possible to determine with reasonable certainty the number of carbohydrate residues in a polynucleotide without relying for calculation on a knowledge of the ratio of purine to

pyrimidine nucleotides in the material under test. It is seen from the Table that the yield of furfuraldehyde from yeast ribonucleic acid is consistent with its formulation as a polynucleotide in which nitrogenous, carbohydrate, and phosphoric acid residues are present in equal numbers. The theoretical recovery of ribose is calculated for purposes of comparison for a tetranucleotide formed from the union of one molecule each of guanylic, adenylic, cytidylic, and uridylic acids.

Having established that the method is applicable to nucleic acids or their derivatives, it was tested next on protein-containing materials which are not suitable for analysis directly by most other methods. These fail either because of the formation of coloured compounds between the reagent used and materials other than furfuraldehyde or because of the production of furfuraldehyde from materials other than pentoses. The latter difficulty is inherent in any technique based on the determination of furfuraldehyde but it was considered possible that the former source of error would not affect the spectroscopic determination of furfuraldehyde, provided that the distillate did not contain other compounds exhibiting appreciable absorption at 278·5 mμ. To test this, the absorption of the steam-distillate from a crude nucleoprotein from beef pancreas was measured between 249 and 298 mμ. The absorption curve fitted exactly that obtained from a distillate from ribose itself and it is concluded that the distillate from the nucleoprotein contained no interfering substances. Furthermore, the protein part of the pancreas material, after being freed from nucleic acids by the method of Sevag, Lackman, and Smolens (*J. Biol. Chem.*, 1938, **124**, 425), gave a steam-distillate exhibiting no specific absorption in this region. Finally, the proportion of pentose nucleic acid present in the crude pancreas nucleoprotein, measured by the method of Schmidt and Thannhauser (*J. Biol. Chem.*, 1945, **161**, 83), was, within the limits of the accuracy of the two procedures, the same as that found by direct analysis for ribose by the modified technique here described.

It is considered, therefore, that providing suitable tests are applied as suggested above, the spectroscopic method for the determination of furfuraldehyde may be applied directly, not only to pentose nucleic acids, but also to nucleoproteins.—THE UNIVERSITY, MANCHESTER, 13. [*Received, March 2nd*, 1950.]

Ethylindole-, 5-Methylindole-, and 5-Methoxyindole-3-carboxylate : a Correction. By G. F. SMITH.

IN a recent publication (*Compt. rend.*, 1946, **222**, 1178), Mentzer claims to have obtained the compounds mentioned in the title by heating aniline, *p*-toluidine, and *p*-anisidine with ethyl formylchloroacetate. Repetition of this work has led to the formation of substances the melting points of which correspond to those of Mentzer's supposed indole-3-carboxylic esters, but which are now clearly identified as ethyl α-chloro-β-aryliminopropionates.

When the reaction between aniline and ethyl formylchloroacetate is carried out at room temperature, a compound of lower melting point is obtained. Since this compound has an ultra-violet absorption spectrum practically identical with that of Mentzer's product, m. p. 82°, has the same carbon and hydrogen content, and can be converted into it by distillation or by repeated crystallisation, it is concluded that the two compounds are geometrical isomers involving the carbon–nitrogen double bond.

Ethyl α-chloro-β-(*p*-methoxyphenylimino)propionate is recovered unchanged after being heated with pyridine or diethylaniline for 5 hours at 100°. The mother-liquors from the crystallisation of the recovered material give no colour on being heated with Ehrlich's reagent, indicating a total absence of indole compounds. Ring closure to an indole, together with very extensive decomposition, does, however, occur when α-chloro-β-(*p*-methoxyphenylimino)propionate is refluxed in diethylaniline for 30 minutes, for the amorphous acid fraction from the saponification of the ether-soluble portion of the reaction product gives a very strong purple colour with Ehrlich's reagent. No attempt has been made to isolate the methoxyindolecarboxylic acid.

Mentzer's claim was precariously based on (*a*) the assumption that, since ring closure to an indole occurs when an arylamine and an ω-bromoacetophenone are heated together, it will also occur when the reaction is carried out with an arylamine and ethyl formylchloroacetate, and (*b*) the nitrogen content of the product of interaction of *p*-toluidine and ethyl formylchloroacetate [Found, 6·2%. Calc. for ethyl 5-methylindole-3-carboxylate, 6·9%. Note that the value calculated for ethyl α-chloro-β-(*p*-tolylimino)-propionate is 5·85%].

Experimental.—Ethyl α-chloro-β-phenyliminopropionate. (*a*) Equivalent proportions of aniline and ethyl formylchloroacetate are heated together at 180° for 5 minutes, and the very dark product distilled *in vacuo*. The fraction, b. p. 175—182°/8 mm., crystallises completely, and the *ester* then separates from ethanol as colourless prisms and from light petroleum as colourless blades, m. p. 80—81° (Found : C, 58·7; H, 5·3; N, 6·45; Cl, 15·4. $C_{11}H_{12}O_2NCl$ requires C, 58·5; H, 5·35; N, 6·2; Cl, 15·7%). Mentzer (*loc. cit.*) gives m. p. 82°. (*b*) A solution of the reactants in ethanol is left for a few minutes at room temperature; crystallisation then occurs on scratching it. The *product* separates from light petroleum as colourless blades, m. p. 68—68·5° (sinters 67°), and from ethanol as colourless slender prisms, m. p. 69° (Found : C, 58·5; H, 5·7. $C_{11}H_{12}O_2NCl$ requires C, 58·5; H, 5·35%). A mixture of high- and low-melting compounds melts at 79—81° (sinters 70°). The same mixture, m. p. 76—79·5°, is obtained when either the high- or the low-melting form is fused and allowed to resolidify. Repeated crystallisation of the low-melting form results in the gradual rise of the melting point to 80—81°.

Ultra-violet absorption spectra.	$\lambda_{max.}$	Inflexion.
Isomer, m. p. 80—81°	316·5 (ε, 29,580)	293 mμ. (ε, 16,030)
Isomer, m. p. 69°	315·5 (ε, 29,850)	293 mμ. (ε, 16,260)

Ethyl α-chloro-β-(p-tolylimino)propionate. Equivalent proportions of *p*-toluidine and ethyl formylchloroacetate react exothermally, and crystallisation occurs on scratching the product. The *ester* is drained by suction and thrice crystallised from ethanol, from which it separates as slender monoclinic prisms, m. p. 95·5—96° (Found : C, 60·3; H, 6·25; Cl, 15·1. $C_{12}H_{14}O_2NCl$ requires C, 60·1; H, 5·9; Cl, 14·8%). Mentzer (*loc. cit.*) gives m. p. 97°.

Ethyl α-chloro-β-(p-methoxyphenylimino)propionate. This *compound*, prepared as above from *p*-anisidine and ethyl formylchloroacetate, separates from ethanol as colourless stout tetragonal crystals, m. p. 96—96·5° (Found: C, 56·4; H, 5·8; Cl, 14·2. $C_{12}H_{14}O_3NCl$ requires C, 56·35; H, 5·5; Cl, 13·85%). Mentzer (*loc. cit.*) gives m. p. 97°.

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A Heterocyclic Perfluoro-compound. By R. N. Haszeldine.

The complete fluorination of hydrocarbons has been achieved using the catalytic, the cobalt trifluoride, and the electrochemical method. In the first, fluorine and the hydrocarbon interact on the surface of a gold- (Haszeldine and Smith, *J.*, in the press) or a silver-plated (Cady, Grosse *et al.*, *Ind. Eng. Chem.*, 1947, **39**, 290) copper catalyst; the second method utilises the fact that cobalt trifluoride, when heated, reacts with a hydrocarbon vapour to replace hydrogen by fluorine and to saturate double bonds by fluorine (Fowler *et al.*, *Ind. Eng. Chem.*, 1947, **39**, 292; Haszeldine and Smith, forthcoming communication); the third method involves electrolysis of a solution of the hydrocarbon in anhydrous hydrogen fluoride (Simons, *J. Electrochem. Soc.*, 1949, 47).

The fluorination of compounds containing nitrogen has received little attention: the electrolysis of pyridine in anhydrous hydrogen fluoride (Simons, *loc. cit.*) yields nitrogen trifluoride and perfluoropentane, and not perfluoropiperidine; Ruff and Giese (*Ber.*, 1936, **69**, 604) have claimed that several isomeric compounds $C_5N_1F_{11}$, which include two compounds with four-membered heterocyclic ring systems, result from the interaction of fluorine and silver cyanide. The complete fluorination of a heterocyclic nitrogen-containing compound has not yet been reported.

The fluorination of 2:6-lutidine has now been investigated. The catalytic and cobalt fluoride methods were used successfully after slight modification to prevent, as far as possible, the formation of the non-volatile hydrofluoride of the dimethylpyridine. A product believed to be *perfluoro-2:6-dimethylpiperidine* has been isolated as a solid, m. p. 94—95° [Found: C, 22·1; N, 3·5; *M* (ebullioscopic), 370. $C_7F_{15}N$ requires C, 21·9; N, 3·7%; *M*, 383], with a characteristic musty odour, which can be purified by sublimation at 50—60°/760 mm. or by recrystallisation from carbon tetrachloride. Perfluoro-2:6-dimethylpiperidine crystallises as large needles and is readily soluble in hot carbon tetrachloride but much less soluble at room temperature; in this respect it resembles perfluorohexadecane, $C_{16}F_{34}$, which, however, crystallises as plates from carbon tetrachloride (Haszeldine and Smith, forthcoming communication).

It is believed that the low yield (*ca.* 5%) of perfluoro-2:6-dimethylpiperidine is caused by formation and subsequent decomposition by fluorination of the hydrofluorides of lutidine and of compounds derived from lutidine by the introduction of one or two atoms of fluorine. Once a certain degree of fluorination has been achieved, however, the basicity of the nitrogen-containing compound is so reduced that hydrofluoride formation cannot occur. Perfluoro-2:6-dimethylpiperidine does not give a precipitate with thorium nitrate solution.

The bulk of the product boils below room temperature and this volatile material is believed to contain fluorocarbons, nitrogenous compounds such as $CF_3{\cdot}NF_2$ and $(CF_3)_2NF$, and possibly nitrogen trifluoride, formed by disruption of the ring.—University Chemical Laboratory, Cambridge. [*Received, March 9th*, 1950.]

The Condensation of Pyrrole-2-aldehyde and Hydantoin. By D. G. Harvey.

5-(2-Pyrrylmethylidene)hydantoin has been envisaged as an intermediate in the synthesis of 2-pyrryl-β-alanine by Herz and Dittmer (*J. Amer. Chem. Soc.*, 1948, **70**, 503) although they were unable to effect the necessary condensation of pyrrole-2-aldehyde and hydantoin in ethanol with catalytic quantities of piperidine. By use of purified reactants and strict adherence to a given time of heating a crystalline compound has now been isolated which gives analytical figures suggesting that it is *5-(2-pyrrylmethylidene)-hydantoin*. So far all attempts to produce the reduced hydantoin by standard methods have been unsuccessful.

Pyrrol-2-aldehyde, (2·0 g.; prepared according to Fischer and Orth, "Die Chemie des Pyrrols," Vol. I, 1934, p. 152, and purified by two recrystallisations), hydantoin (2·4 g.), redistilled piperidine (2 ml.), and absolute ethanol (20 ml.; distilled over sodium) were boiled under reflux for 1 hour. After removal of most of the solvent *in vacuo*, and acidification to litmus by dilute acetic acid (10% v/v) a yellow crystalline solid separated (2·5 g., 73%). It was recrystallised with some difficulty from aqueous-ethanolic pyridine (1:1:1) in yellowish-brown needles, m. p. 228—230° (Found: C, 54·0; H, 4·07; N, 23·2. $C_8H_7N_3O_3$ requires C, 54·2; H, 3·95; N, 23·7%. Analysis by Drs. Weiler and Strauss, Oxford).

The work was performed in the Department of Physiology, Royal Veterinary College.—Department for Research in Industrial Medicine, M.R.C. Laboratories, Hampstead, London, N.W.3. [*Received, March 10th*, 1950.]

Mechanism of the Benzidine Rearrangement. By E. D. Hughes and C. K. Ingold.

This subject has been discussed by Ingold and Kidd (*J.*, 1933, 954), and Hughes and Ingold (*J.*, 1941, 608); who assumed conjugative electron displacements from *p*- to *p'*-positions in an intermediate state of the formation of the univalent cation (I); by Robinson (*J.*, 1941, 220), who postulated similar displacements (not reversed, as Dewar has stated) in fully-formed (I); and also by Hammick and Mason (*J.*, 1946, 639),

who interrupted the conjugation in order to include an extra angle in the structure (but not a boat-shaped ring, as Dewar has asserted), thus bringing the *pp'*-positions nearer; and finally by Dewar (*J.*, 1948, 406, 777; *Disc. Faraday Soc.*, 1947, **2**, 50; "Electronic Theory of Organic Chemistry," Oxford, 1949, p. 235), who transfers the charge in (I) to the neighbouring ring, which he then allows to take in electrons from the other ring, thus establishing a " σ-bond."

(I.) $PhN\overset{+}{H}_2{\cdot}NHPh$ $PhN\overset{+}{H}_2{\cdot}\overset{+}{N}H_2Ph$ (II.)

Hammond and Shine (*J. Amer. Chem. Soc.*, 1950, **72**, 220) have recently adduced evidence that the rearranging entity is the bivalent cation (II), a finding which seems to us to allow a solution of all the main difficulties. The original difficulty, which made Kidd, Hughes, and Ingold refuse to contemplate fully-formed (I) as the rearranging entity, *viz.*, that of moving electrons from a positive nitrogen atom to a neutral one, is overcome by making the second nitrogen atom positive. Then, (II) has adjacent charges, which can plausibly be supposed so to weaken the N–N-link that its electrons can functionally conjugate (or "hyperconjugate") with the aromatic π-electrons, thereby completing the internuclear conducting system. This could enable near-integral charges to be built up in the *pp'*-positions; and, even though the minimum separation of these positions would be about 4·2 A. in strainless (II), this is not too great a distance for the establishment in (III) of a fairly strong electrostatic (or mainly electrostatic) bond; which, as the unlike charges come together and the like charges separate, would smoothly go over into a covalency in the product of the rearrangement.

(III.)

—UNIVERSITY COLLEGE, LONDON, W.C.1. [*Received, March 31st*, 1950.]

OBITUARY NOTICE.

T. SLATER PRICE, F.R.S.

THOMAS SLATER PRICE was born on August 24th, 1875, and died on October 29th, 1949. Educated at King Edward's High School, Birmingham, he proceeded to Mason College, Birmingham, and graduated with first-class honours in chemistry and physics at the University of London in 1895. In that year he was appointed Priestley Research Scholar in chemistry at Mason College and in the following year, as an 1851 Exhibition Scholar, he moved to Leipzig to study under Professor W. Ostwald. Graduating Ph.D. "*summa cum laude*" in 1898, he studied for a further year in Professor Arrhenius's laboratory at Stockholm.

On returning to Britain in 1900, he was appointed honorary lecturer in chemistry at Mason University College, and in the following year he went to University College, Sheffield, as assistant lecturer. After two years as senior lecturer in chemistry at the University of Birmingham, he was appointed Head of the Chemical Department of the Birmingham Central Technical College in 1903, a post which he held until 1920. Under his direction the work in this Department was completely re-organised and extended, and, although his energies were very fully occupied in teaching and organisation, he was able to carry out a large number of researches on per-acids, organic disulphides, and complex metal ammines, the results of which are embodied in some forty papers published during this period. For his work he was awarded the degree of Doctor of Science of the Universities of London and Birmingham.

In April 1916, Slater Price was commissioned as lieutenant, R.N.V.R., in order to take up special chemical work of a secret nature at the Royal Naval Experimental Station, Stratford, and later he was put in charge of all the chemical and technical work of this Station and promoted lieutenant-commander. Among the many problems which were studied under his direction at this time was the devising of materials for making smoke screens such as were used in the Zeebrugge raid.

Early in 1920 he was appointed director of research to the British Photographic Research Association. Under his able direction and inspiration, a long list of papers was published year by year from the laboratories of the Association until it closed down in 1930. He was appointed to the chair of chemistry in the Heriot-Watt College, Edinburgh, in 1931, and retired in 1940.

Slater Price was a member of the General Council of the Royal Institute of Chemistry during 1911—14 and 1921—24, and served as Vice-President during 1924—27. Keenly interested in the training of young chemists, he was largely responsible for the initiation of the scheme for National Certificates in Chemistry. In 1921 he was elected to the Council of the Chemical Society and served as its Senior Secretary during 1924—28, as Honorary Treasurer during 1928—31 and as Vice-President, 1931—34.

He was a Fellow of the Royal Photographic Society, a member of the Council of the Society, 1922—31, and Vice-President, 1926—29. He was an Hon. Member of the "Société Française de Photographie."

He was gazetted an Officer of the Order of the British Empire (Military Division) in 1919 and elected a fellow of the Royal Society of London in 1924 and of the Royal Society of Edinburgh in 1932.

Since his retirement, Slater Price had been in very poor health, and those who watched him during these later years could not but be impressed by the patient fortitude and inner peace with which he bore his increasing physical limitations. The death of his beloved wife a little more than a year ago was a loss which he felt most keenly, for she had nursed him with loving care in his great weakness.

Professor Slater Price was a man of outstanding gifts of mind and insight. His clear and definite faith in the reality of God was the mainspring of his life, enabling him in the days of his health to serve his Church loyally and devotedly, and all his days to inspire those who met him in scientific circles or in private life.

HUGH B. NISBET.

PRESIDENTIAL ADDRESS.

DELIVERED BEFORE THE CHEMICAL SOCIETY IN EDINBURGH ON MARCH 29TH, 1950.

The Chemical Society—A Mid-century Review.

By SIR IAN HEILBRON, D.S.O., D.Sc., LL.D., F.R.S.

INTRODUCTORY.

IN selecting the title for this Presidential Address, although by no means creating a precedent, I am departing from a custom which has prevailed in recent years. In doing so I make no apology, for I feel that it is useful for the President from time to time to survey the affairs of the Society and of Chemistry in the course of his Address.

In the early years of the Society's history such Addresses were regularly delivered, and the tradition was last upheld by Sir Gilbert Morgan in 1934. Since then much has transpired. The country is slowly recovering from six years of war, which have left their mark on science as on every other phase of our national life.

So far as chemistry is concerned, its importance as a dominant factor in re-establishing the prosperity of the country is generally recognised. In many ways the growing appreciation of Chemistry's function in the modern State has added to the difficulties which face the Society. These difficulties are familiar enough to our senior Fellows, but those who have been more recently elected—and our Fellowship has doubled in ten years—may not be so well acquainted with them.

Although my remarks deal primarily with the domestic affairs of the Society, I shall also refer to our external relations both with other British chemical organisations and with the International Union of Pure and Applied Chemistry.

GOVERNMENT AND ORGANISATION OF THE SOCIETY.

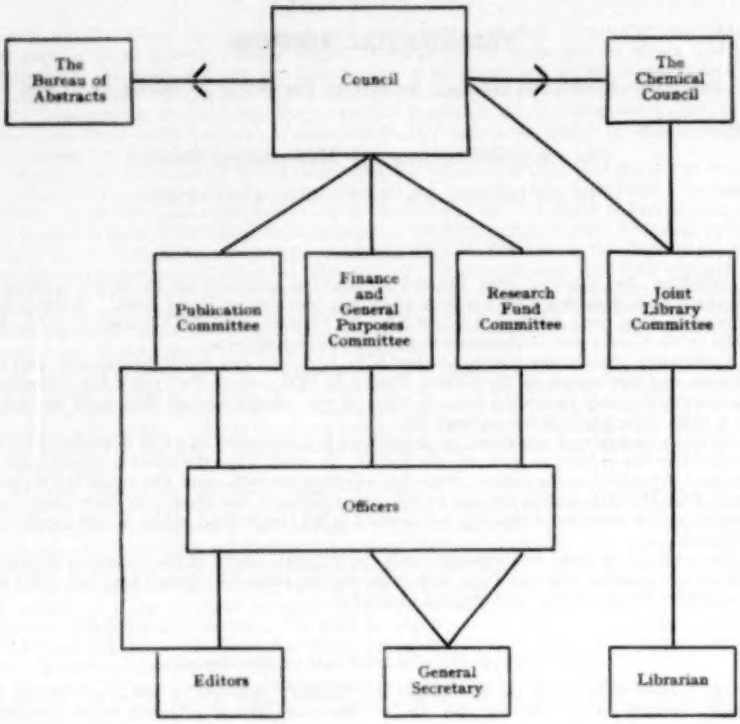
The Society is governed by its Council, the Ordinary Members of which are elected by Fellows resident in the British Isles for a three-years period of office on a territorial representation basis. The general administration is supervised by the Officers (President, Treasurer, and Honorary Secretaries), who generally meet weekly throughout the working session and act as a Board of Directors responsible to Council through the Finance and General Purposes Committee, the Publication Committee, and the Research Fund Committee (Fig. 1). In all these activities the central part played by our General Secretary must not be overlooked, for it is upon his shoulders that much of the day to day responsibility devolves. We are indeed fortunate in having this important office filled by a person so capable and enthusiastic as Mr. Ruck Keene. The Council is also responsible for the capital expenditure on the Library, which is authorised on the recommendation of the Joint Library Committee. This latter is an organ of the Chemical Council and represents all the bodies whose members have been granted the right to make use of the Library.

In 1932 a long overdue extension of the Society's activities was brought about by the appointment of Local Representatives at seventeen centres throughout the country. At the present time there are 30 such Representatives covering the British Commonwealth, including Representatives from Ceylon, India, and Pakistan whom we have recently added.

Many Fellows will not realise how much they are indebted to those who have served the Society as Honorary Officers, as members of Council or of its Committees, or as Local Representatives, and in other ways. The growth of the Society and the high reputation of its publications are due in no small measure to the fact that throughout its history the Society has never lacked Fellows willing to place their time and experience freely at its disposal.

FIG. 1.

THE CHEMICAL SOCIETY



FELLOWSHIP.

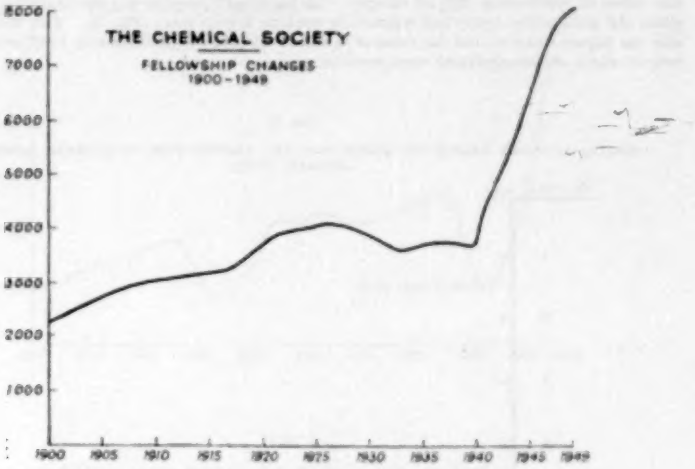
The membership of our Society—77 in 1841—had increased to 2292 by 1900. Its further expansion since that date provides an index of the growth of chemistry as a science. This is shown diagrammatically in Fig. 2, which also reveals, in its minor fluctuations, the political and economic vicissitudes of the past half-century. By 1910 the Fellowship had grown to over 3000, but with the First World War, when this country was forced to develop an organic chemical industry as a matter of urgent necessity, the rate of increase became more rapid, only to be slowed and then reversed by the years of depression between the wars. In the later "thirties" our numbers again showed modest increases and received only slight set-backs at the outbreak of war in 1939. From 1941 onwards, however, the membership curve has risen very steeply, passing the 8000 mark in 1949.

This is due, in part, to the joint subscription scheme, to which I will refer in detail later. Much of the increase of recent years, however, can be ascribed to the accelerated expansion of chemical activity attributable first to the needs of war and now to those of increased productivity.

Can we expect this increase to continue? On the one hand, we must remember the experiences of the 1920's, when the end of the post-war boom led to a decline in numbers. On the other

hand, the supply of trained chemists, who are in greater demand than ever before, has not yet reached its peak and, as is shown in a report recently issued by the Ministry of Labour and

FIG. 2.



National Service, the output of graduates with chemical training over the next five years will, in spite of the expansion in training facilities that has taken place, fall short of the demand by nearly 2000 chemists. The same report estimates that nearly 10,000 trained chemists will be required over the next five years to meet an expansion in the Chemical Industry, in the Scientific Civil Service, and in teaching appointments. We have, therefore, solid grounds for believing that the chemical community as a whole is in a reasonably strong position to meet any difficulties of readjustment that may arise during the next few years. Beyond that it would be rash to attempt to prophesy.

THE SOCIETY'S PUBLICATIONS.

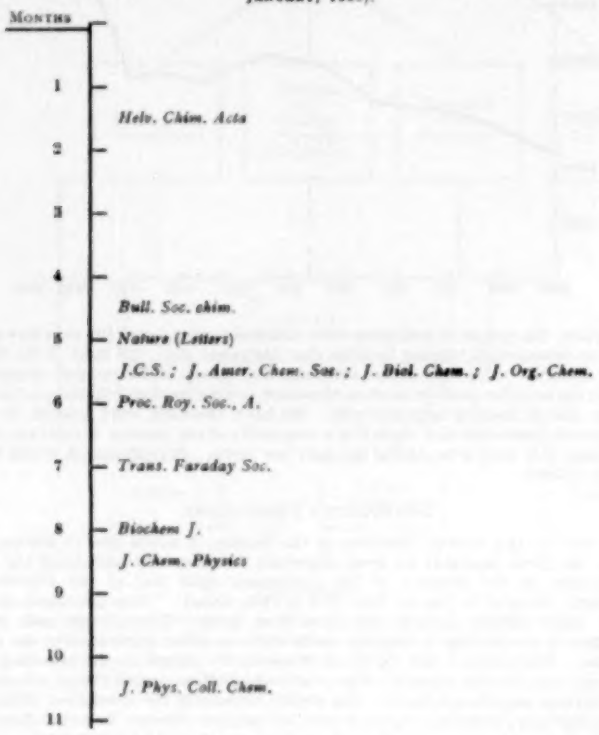
Turning now to the various activities of the Society, I would like to discuss first our publications, for these represent its most important function. In addressing the American Chemical Society on the occasion of the conferment upon him of the Priestley Medal, Dr. A. B. Lamb, Editor of its Journal from 1918 to 1949, stated: "New discoveries that remain undisclosed might almost as well not have been made. The prompt and widespread communication of new findings is essential, particularly to fellow scientists who can appreciate and use them. Publication is the life-blood of science." Judged by this standard, we have, I submit, every reason to be satisfied. The *Journal* for 1949 contained 870 papers and was the largest the Society has ever produced. The steady increase in the circulation of the *Journal*, coupled with the very favourable reception given to *Quarterly Reviews*, first introduced in 1947, indicate that the quality of our publications has been maintained at a high level.

A rapidity of publication almost approaching the pre-war rate has now been reached, no mean achievement when one bears in mind that only two years ago a paper submitted for publication would not appear in print for some twelve or thirteen months. It is unnecessary to elaborate how such a delay in publication must seriously hamper further development and application of any research. To-day, thanks to the vigorous policy of the Publication Committee and the unremitting energy of the Editorial Staff and Messrs. Richard Clay and Company, our Printers, the Society is publishing papers received, in most cases, only four months previously—a rate of publication which, as indicated in Fig. 3, compared, already in January, very favourably with that of other chemical journals.

The impact of chemistry on the economic life of the country is reflected in the increase in volume of the scientific communications published by the Society, which has risen by over 500% during the past half-century (Fig. 4). It will be observed that, with only minor fluctuations, a steady rise took place up to the period of the First World War, when, as again in 1939—1945, the curve of publication dipped steeply. Of particular interest are the statistics since 1943, when the publication curve had reached its wartime lowest point (Fig. 5). This diagram shows also the papers received and the manner in which the rate of publication in 1949 outstripped the rate at which communications were received.

FIG. 3.

MONTHS BETWEEN RECEIPT OF MANUSCRIPT AND DISTRIBUTION OF JOURNAL (AVERAGES—JANUARY, 1950).



Although it is obviously difficult to attempt to forecast the size of the *Journal* in future years, the rate at which papers have been submitted during the past twelve months and are still being submitted suggests that it will be necessary as a permanent service to publish a much larger *Journal* than before the war. There are various factors which support this view: the more enlightened attitude towards publication adopted by industrial firms; the proliferation of Government-sponsored research organisations; and the opening of new centres for research in the Dominions and throughout the Commonwealth. Again, we must not overlook the expansion of post-graduate research in all University Departments of Chemistry. While papers coming

FIG. 4.

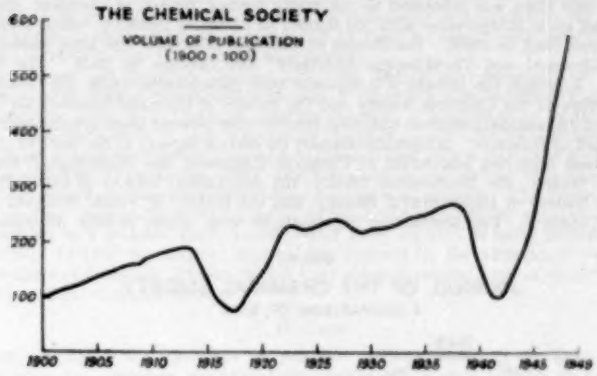
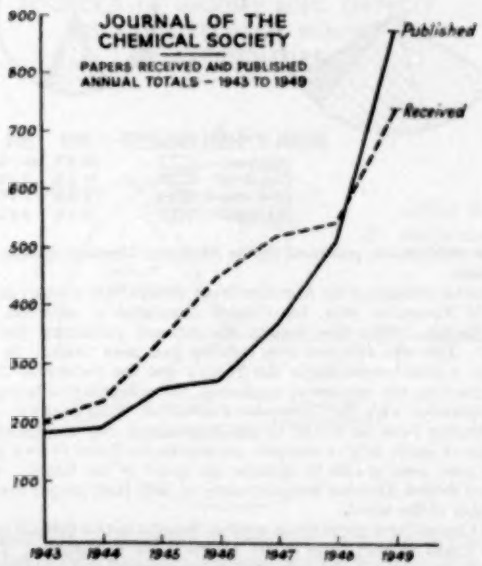

THE CHEMICAL SOCIETY
VOLUME OF PUBLICATION
(1900 = 100)
600
500
400
300
200
100
1900
1905
1910
1915
1920
1925
1930
1935
1940
1945
1949

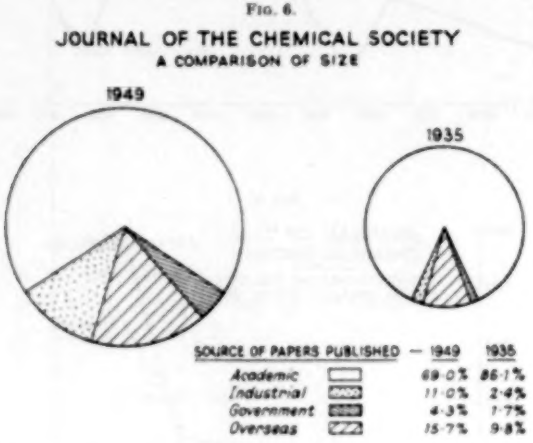
FIG. 5.


JOURNAL OF THE CHEMICAL SOCIETY
PAPERS RECEIVED AND PUBLISHED
ANNUAL TOTALS – 1943 TO 1949
Published
Received
900
800
700
600
500
400
300
200
100
1943
1944
1945
1946
1947
1948
1949

from academic sources still provide the major contribution to our *Journal*, the proportion from industry, from Government sources, and from overseas has more than doubled in the past fifteen years (Fig. 6).

Abstracts.—The Society issued a regular series of Abstracts in its *Journal* from 1871 until 1924, when this work was delegated to the newly formed Bureau of Chemical Abstracts—a joint body set up in co-operation with the Society of Chemical Industry, whose publication of Abstracts dates back to 1882. The Bureau of Chemical Abstracts was later known as "The Bureau of Chemical and Physiological Abstracts" and became, in 1945, "The Bureau of Abstracts." Although the Bureau is a separate body incorporated under the Companies Act of 1929, it relies on the Chemical Society and the Society of Chemical Industry for by far the greater part of its financial resources, and these two Societies between them appoint approximately half the Board of Directors. Additional support for certain aspects of the work of the Bureau is now received from the Institution of Chemical Engineers, the Physiological Society, the Pathological Society, the Biochemical Society, the Anatomical Society of Great Britain and Ireland, the Society of Experimental Biology, and the Society of Public Analysts and other Analytical Chemists. The abstracting organisations with which *British Abstracts* may be

FIG. 6.



compared are *Chemical Abstracts*, published by the American Chemical Society, and the German *Chemisches Zentralblatt*.

In times of financial stringency the Abstracts have always been a ready target for economy measures. Thus, in November 1924, the Council considered a resolution in the name of Professor W. H. Perkin "That the Society discontinues publishing the Abstracts from 1st January 1926." This was defeated after a ballot had been taken. In 1931, the period of the world slump, a joint committee of the Society and the Society of Chemical Industry explored, without reaching any successful conclusion, the possibility of bilingual Abstracts to be produced in co-operation with the *Chemisches Zentralblatt*. The question of the Abstracts is again before us. During 1949, as stated in the Proceedings, the Council was unfortunately forced, owing to lack of funds, to give absolute priority to the Society's own publications. As a consequence, we have been unable to increase our grant to the Bureau, which must have more financial help if *British Abstracts* are adequately to fulfil their proper function of covering the chemical literature of the world.

The Officers and Council have given much anxious thought to this difficult question, to which an answer must be found without delay if our Abstracts are to continue. I believe that the ultimate solution is to be sought in the formation of an international abstracting organisation, and I hope that this pressing problem will figure prominently on the agenda at the XVIth Conference of the International Union of Pure and Applied Chemistry which meets next year in the United States. Our friends of the American Chemical Society are, I believe, also not

entirely free from financial anxieties regarding their publications, and I suggest that official talks should be initiated with them without delay in order to examine the possibilities of common action. It is therefore with mixed feelings that I read of the revival of the *Chemisches Zentralblatt*. Apart from financial considerations, the duplication of abstracts in various countries places an intolerable burden on scientific manpower, and cannot to-day be justified.

We claim that science is international. Let us then go ahead with determination and imagination to carve a way to successful co-operation.

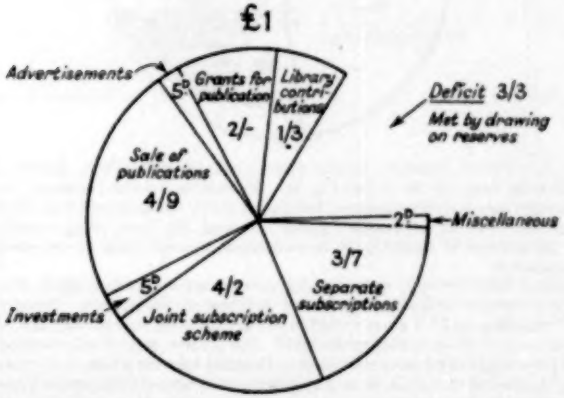
Annual Reports and Quarterly Reviews.—In 1904, during the Presidency of Sir William Tilden, the series of *Annual Reports on the Progress of Chemistry* were instituted to fill a need for special reports, in addition to abstracts, defining the state of knowledge on particular fields of research. With the growth of new branches of chemistry, each with its specialised language and techniques, it became impossible for one reporter to deal with a subject of such wide range as, say, General and Physical Chemistry, and the practice was started of inviting specialists to write short reviews on selected topics judged ripe for summarising. This measure, excellent in itself, was not sufficiently comprehensive to meet the demand for reviews on specialist subjects written in a manner which would render them capable of being understood by the non-specialist. In 1947 the Society, after a delay imposed by the outbreak of war, published the first volume of *Quarterly Reviews*, which have since developed into an important item in the Society's range of publications.

Finance.

In financial affairs, the situation, as you will have gathered, is far from satisfactory, especially when one considers the important services the Society renders to the State and Industry alike. The exceptional increase in the volume of publication has for the last two years

Fig. 7.

SOURCES OF INCOME AND DEFICIT RELATED TO EACH POUND OF EXPENDITURE



prevented the Society from balancing its accounts. Our total income—excluding special funds—was £48,244 in 1949, showing a deficit of income over expenditure of £9,111.

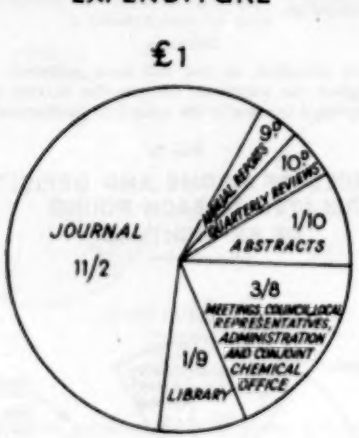
The source of every pound of our income is conveniently reproduced in a simple form of diagram sometimes known as the "Industrial Cake" (Fig. 7). Unfortunately, the Society's cake starts with a goodly slice missing, *i.e.*, the deficit which we have had to make good by drawing on our all too slender reserves. It will be seen that Fellows of the Society and

subscribers to our publications find nearly three-quarters of our total income and that grants from outside sources represent only one-tenth of the total.

The diagram of our expenditure (Fig. 8) reveals how high a proportion of our resources is devoted to publications. One of the problems which has always beset the Society is how to supply the younger chemists with the *Journal* at a moderate price. It is no more reasonable to expect them to pay the full cost of the *Journal*—an essential tool of their trade—than to expect a worker to pay for the expensive machine which he operates for the benefit of his country or of his firm. For this reason, the Council has taken steps to ensure that the recent increase in schedule prices should fall less heavily upon the younger chemists paying the reduced subscription.

In 1841 the annual subscription was fixed at £2 for town members and £1 for country members, a distinction which was later dropped. The basic subscription was increased to £3 in 1921 and to £3 : 10 : 0 in 1947, but this did not affect Fellows under 25 years of age, for whom the subscription was retained at £1 : 15 : 0. Few Societies, I should imagine, are able to show so small an increase in subscription over so long a period.

FIG. 8.



Naturally, if a Fellow wishes to receive every available publication, he will obviously pay much more than the basic £3 : 10 : 0 (see Fig. 9). Even in such a case, however, it cannot justly be claimed that the cost is really excessive, having regard to the increased bulk of all publications and to the general rise in commodity prices. Indeed, far from being overcharged for his publications, the chemist in this country receives them in some cases at considerably less than the cost of production.

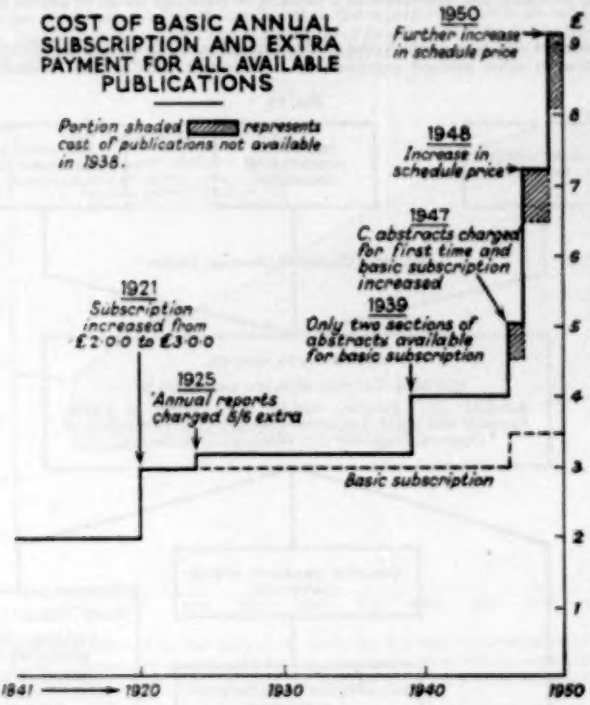
Unfortunately, there are still those among us who are satisfied to enjoy the benefits and privileges of a profession without contributing anything to its upkeep. Even at the risk of being called "old-fashioned," I must record my belief that the younger chemist of to-day lacks the "esprit de corps" of an earlier generation. The present annual subscription represents a much smaller percentage of a young man's salary than did the sum which, fifty years ago, Fellows of the Society considered it an honour to pay. I have no time for the person who refrains from supporting the Society because he has access to all the journals in a library. No intellectual pursuit can be followed on the basis of a rigid time-table of study, and many will agree with me that they can gain much more from a leisurely perusal of journals in their own homes. But if ties of duty and sentiment are not so strong to-day, surely self-interest should dictate the necessity for young men in chemical appointments to play their part in the affairs of the Society in the advancement of their science. I would like to see every chemical firm make it an obligation that all qualified chemists employed by them should contribute through the Chemical Council

to the services provided for the benefit of chemists as a whole. If this were done, the status of chemists in the community would very soon be raised and most of the financial problems of the publishing bodies would rapidly disappear.

Before I deal with the part which the Society plays on the Chemical Council and, through the British National Committee for Chemistry, in international affairs, I should make mention of the more important of the special funds which the Society controls.

The Research Fund was formed in a small way as early as 1872 and was later considerably augmented by donations from Dr. G. D. Longstaff, the Worshipful Company of Goldsmiths, and others. The annual income of the Fund is now some £600—700, and grants for the purchase of

FIG. 9.



special apparatus and chemicals are awarded twice per annum. This Fund is greatly appreciated by workers in many academic institutions, especially those with slender resources.

The Centenary Fund, inaugurated during the celebrations in 1947, enables us to strengthen our age-long ties with our foreign colleagues. The Fund exists to defray the cost of inviting distinguished chemists from overseas to lecture in this country and to take part in our meetings. It also enables the Society to send official delegates to conferences and meetings in other countries.

The Chemical Council.

The increasingly heavy cost of publication had earlier in this century become a burden too great for the Society to meet from the subscriptions of its Fellows alone, and this was recognised in 1925 when, somewhat tardily, Industry contributed a sum of just over £2,000 to the Publications Fund, which had just been instituted largely through the energies of the Treasurer

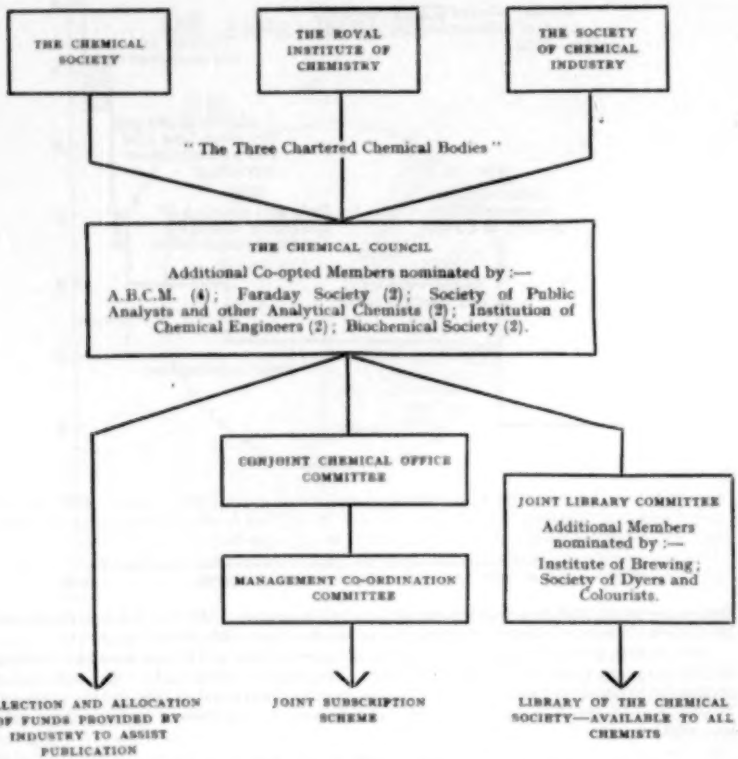
at that time, the late Sir Jocelyn Thorpe. In contributing to this Fund, and in making further donations to the cost of publications in subsequent years, Industry formally acknowledged the essential services which the Chemical Society and the Society of Chemical Industry provided.

The need to co-ordinate the assistance given by Industry led to the formation of the Chemical Council in 1935 by deed of agreement between the three chartered chemical bodies—The Chemical Society, The Society of Chemical Industry, and The Royal Institute of Chemistry. In the words of the agreement, the objects of the Council were

> "co-ordination of scientific and educational publications, the publication of new discoveries in chemical science and of their application to the arts and manufactures, the promotion of research, the maintenance of a library for research and education purposes, and the provision and equipment of a building or buildings for all or any of the aforesaid purposes."

The agreement also gave power to the newly formed Council to co-opt as additional members representatives of other kindred organisations. At present, the Chemical Council consists of

Fig. 10.

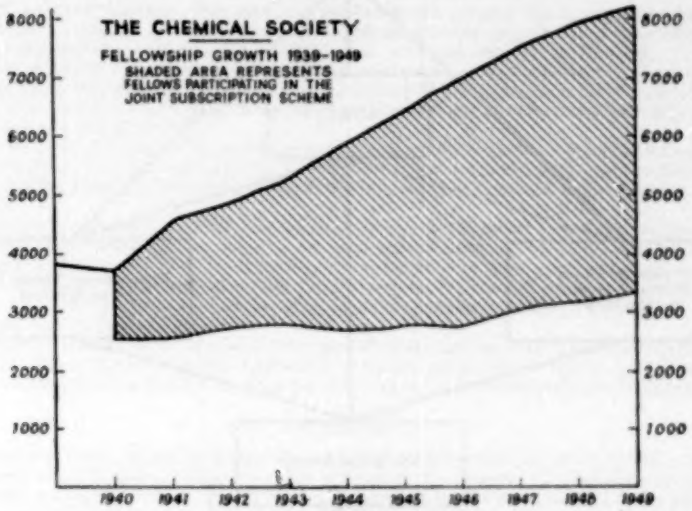

THE CHEMICAL SOCIETY
THE ROYAL INSTITUTE OF CHEMISTRY
THE SOCIETY OF CHEMICAL INDUSTRY
"The Three Chartered Chemical Bodies"
THE CHEMICAL COUNCIL
Additional Co-opted Members nominated by :—
A.B.C.M. (4); Faraday Society (2); Society of Public Analysts and other Analytical Chemists (2); Institution of Chemical Engineers (2); Biochemical Society (2).
CONJOINT CHEMICAL OFFICE COMMITTEE
MANAGEMENT CO-ORDINATION COMMITTEE
JOINT LIBRARY COMMITTEE
Additional Members nominated by :—
Institute of Brewing; Society of Dyers and Colourists.
COLLECTION AND ALLOCATION OF FUNDS PROVIDED BY INDUSTRY TO ASSIST PUBLICATION
JOINT SUBSCRIPTION SCHEME
LIBRARY OF THE CHEMICAL SOCIETY—AVAILABLE TO ALL CHEMISTS

twenty-four members—four from each of the three chartered bodies and from the Association of British Chemical Manufacturers, and two each co-opted from the Faraday Society, the Society of Public Analysts and other Analytical Chemists, the Biochemical Society, and the Institution of Chemical Engineers (Fig. 10).

The agreement constituting the Chemical Council made special provision for the management of the Library of the Chemical Society to be in the hands of a Joint Library Committee responsible to the Council, and for the maintenance of the Library to be shared between the constituent bodies in proportion to their membership. The capital expenditure on journals, books, fixtures, and binding is, however, still borne entirely by the Chemical Society, which retains its ownership of the Library and its contents.

A further important activity of the Chemical Council has been the inauguration of the Joint Subscription Scheme, now administered by the Conjoint Chemical Office. The Scheme has been a considerable boon to its participants, since it has enabled those with very varied interests to select the services suited to their individual requirements from a wide range provided by more than one Society. The chemist is able to obtain these services, which may vary at different stages of his career, at much less cost than the separate subscriptions to the individual bodies. At the same time, he has the satisfaction of knowing that he is playing his part in maintaining the services required by the chemical community as a whole.

FIG. 11.



Benefit has also accrued to the respective Societies through the operation of the Scheme. Although many factors have contributed to the increase in membership over recent years, we must not overlook that a high proportion of the Fellows now pay a joint subscription, as shown in Fig. 11.

Since the formation of our Society in 1841 chemists have founded a number of societies and institutions to provide for their special interests. In part, this has arisen since it would be difficult for one body to cater for the needs of all the specialised branches of chemistry. Each of these bodies has developed a character of its own and has its own group of loyal supporters. At the same time, it must be admitted that chemistry suffers by comparison with some other professions which have a strong central organisation to control their scientific, professional, and technological interest. Can we not, I wonder, build on the Joint Subscription Scheme an organisation that will give us the benefits of centralised control, while retaining for the various Societies an autonomy in the conduct of their affairs?

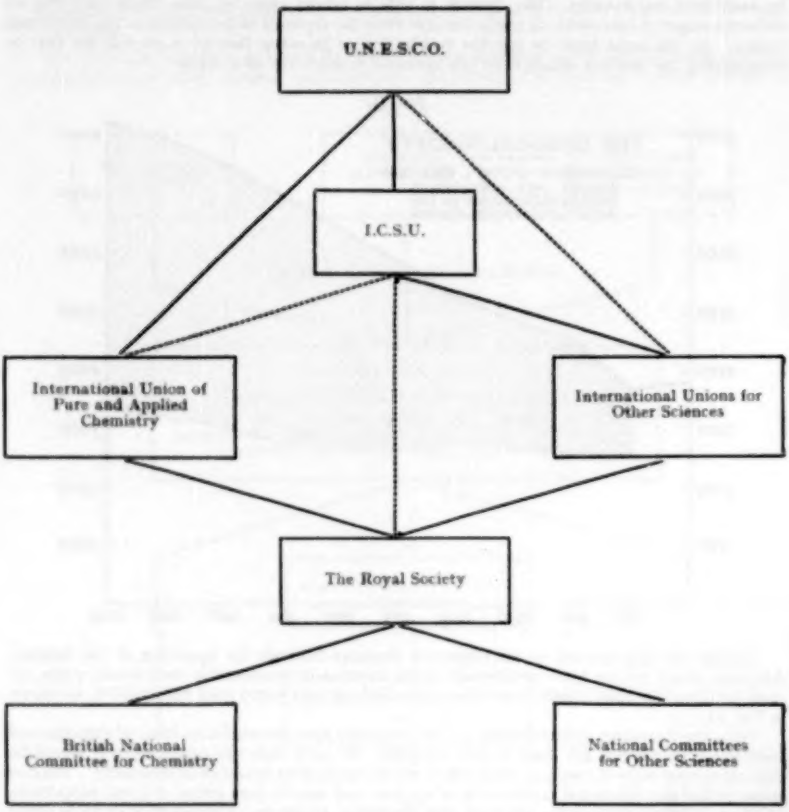
In the meantime, the Chemical Council has launched a new appeal to Industry to increase the support which it has given in the past and without which it is impossible for the publishing societies to render a full service to the welfare of the country. Although it is too early to measure the result of this appeal, we earnestly hope that it will enable our publications to

continue without restrictions, from which the Chemical Industry would be the first to suffer, to the ultimate detriment of our whole national economy.

International Union of Pure and Applied Chemistry.

I have already mentioned the International Union of Pure and Applied Chemistry. As there seems to be little general knowledge among the majority of chemists in this country concerning this body, I would like, before concluding my address, briefly to refer to its activities and its relationship with our Society (see Fig. 12).

Fig. 12.



Historically, I have to go back to 1918, when the Royal Society, the Académie des Sciences of Paris, and the National Academy of Sciences at Washington discussed informally a possible future organisation of scientific undertakings. A preliminary meeting was held in London in October, 1918, on the invitation of the Royal Society, at which eight of the Allied countries were represented. This was followed by an official meeting of delegates from the academies of the Allied countries and, in the case of Great Britain, the Royal Society, which met in Brussels in the summer of 1919 as the first General Assembly of the International Research Council. At this Assembly, International Unions for Astronomy, Geodesy and Geophysics, Chemistry, and

Mathematics were formed and their Statutes were approved, as well as those of the Research Council (I.C.S.U.). The Unions were left completely free to manage their own affairs in accordance with their Statutes, and from the outset the International Union of Pure and Applied Chemistry has been the most active and has worked most satisfactorily.

Thirty-one countries are now attached to the Union, which is governed by a Council consisting of delegates from all the adhering countries. The number of delegates each country can nominate depends on the category in which it is placed according to its importance in the field of chemistry. There are three categories. Countries comprising category A have the right to nominate six delegates, category B four delegates, and category C two delegates. In the case of Great Britain, which naturally comes within category A, delegates are appointed by the Royal Society working through its National Committee for Chemistry, upon which the Chemical Society is represented.

While the Council is the supreme controlling body of the Union, executive powers are vested in a General Purposes Committee known as the Bureau. This Committee consists of the President, six Vice-Presidents, six elected members, the Treasurer, and the General Secretary. A meeting of the Council and of the Bureau constitutes a Conference, which meets every two years in a selected country. The agenda of the Conference includes the Presidential Report, the Treasurer's Report, general administrative business, and the reports of the Commissions. These Commissions cover all the scientific and technical aspects of chemistry. Each Commission has its own chairman and secretary, and is composed of specialists in the specific field for which it has been set up. There are at present 20 Commissions, detailed information on the work of which will be found in the issues of *Chemistry and Industry* dated February 25th and March 4th and 11th, 1950.

Recently, I.C.S.U. has set up mixed Commissions, which are composed of delegates from more than one Union. An example of this is the Commission on Standards, Units and Constants of Radioactivity, which includes delegates from the International Unions of both Chemistry and Physics.

During the meeting of the XIVth Conference of the International Union of Chemistry in London in July, 1947, it was decided to set up a small Executive Committee selected from members of the Bureau. The Executive Committee meets every three months to carry out the routine business of the Union; at present its members are Professor H. R. Kruyt (President), Dr. L. H. Lampitt (Treasurer), Professor R. Delaby (Secretary General), Professor Sir Ian Heilbron, and Professor E. Berner.

Finally, I should explain in a word that apart from the International Union's own income, which is used to defray travelling expenses of delegates, publication of reports, etc., financial aid is provided by U.N.E.S.C.O. towards the cost of meetings of Commissions and Conferences.*

Conclusion.

Chemistry is playing an indispensable part in the complex economic life of to-day. Some of its achievements arouse widespread public interest, as, for example, the production of nylon, penicillin, or cortisone, but the steady flow of chemical discoveries in other fields is not always appreciated. New materials with special properties, new solvents, new drugs, and new dyestuffs are always being made available through chemical research for use in industry, and the service which the Chemical Society can render to the research worker, especially by the provision of a rapid and efficient medium for the publication of his results, was never greater than it is now.

Furthermore, international organisations are likely to play an increasingly important rôle in the future and, by establishing agreed standards and possibly by the co-ordination of abstracting services, will do much to make it easier for work performed in one country to be understood and applied elsewhere. The Society can, however, only fulfil its task in the national and the international sphere if it has the full support of its Fellows and, moreover, if all chemists regard membership of the Society as a primary duty.

One final word, which is to express my warm thanks to Mr. Ruck Keene for the unsparing help he has given me in the preparation of this address.

* For detailed information regarding the formation of the International Union of Pure and Applied Chemistry, see the late Sir Henry Lyons's book "The Royal Society 1660—1940;" also "International Organisation of Chemists" by Marston Taylor Bogert, *Chem. Eng. News*, 1949, **27**, 1992, and "The International Union of Pure and Applied Chemistry," by R. Delaby, *Endeavour*, 1950, **9**, 16.

ONE HUNDRED AND NINTH ANNUAL GENERAL MEETING.

THE One Hundred and Ninth Annual General Meeting of The Chemical Society was held in the Chemistry Department, King's Buildings, West Mains Road, Edinburgh, at 12 noon on Wednesday, 29th March, 1950. The President, Sir Ian Heilbron, was in the Chair.

The notice convening the Meeting was read.

The Report of Council for 1949 which had been circulated to Fellows attending the Meeting was presented by Professor D. H. Hey who referred to the continued growth of the Society during the past year. Although this was satisfactory, he warned that the "turnover" of Fellows was higher than in the past and it was important to lose no opportunity of recruiting new Fellows for the Society.

He referred also to the increase in the size of the *Journal* and to the satisfactory progress in reducing the delays of publication. By the purchase of back numbers, and by arrangements for reprinting the early volumes of the *Journal*, the Society would shortly be able to supply almost a complete set of back issues of the *Journal* from 1848.

In presenting the Accounts for 1949, the Treasurer stated that the expenditure for the year exceeded income by over £9000. This was almost entirely due to the growing expenditure on publications. Had not the Council taken steps during the year to increase revenue, the deficit would have been considerably larger. The Special Reserve Fund would meet the loss for 1949; but that part of the Fund allocated for Publications was now exhausted and, if expenditure was to continue at the present level and publication was not to be curtailed, the Society must increase its income. An appeal to Industry had been launched by the Chemical Council and the Treasurer hoped that support would be forthcoming on a scale sufficient to balance the increased expenditure.

Dr. Neil Campbell proposed the adoption of the Report of Council and the Accounts, and his motion was seconded by Dr. M. Ritchie and carried unanimously.

The following elections to vacancies on Council were announced:

President:

Professor E. K. Rideal.

Vice-President:

Professor R. P. Linstead.

Elected Ordinary Members of Council:

Constituency I:

Dr. J. S. Anderson.
Dr. L. N. Owen.

Constituency IV:

Professor F. E. King.
Professor L. Hunter.

On the motion of Dr. Duncan Taylor, seconded by Dr. G. Aspinall, Messrs. W. B. Keen & Co. were re-appointed Auditors to the Society for 1950.

At the conclusion of the Meeting, a vote of thanks to the Officers and Council, Local Representatives, and others who had served the Society during the year, was proposed by Professor E. L. Hirst, seconded by Dr. T. R. Bolam, and carried with acclamation.

The formal induction of Professor E. K. Rideal as President of the Society took place at the Anniversary Dinner of the Society held on Thursday, March 30th, at the North British Station Hotel, Edinburgh.

REPORT OF COUNCIL FOR 1949.

I. FELLOWSHIP.

1. *Honorary Fellowship.* The following were elected Honorary Fellows of the Society in 1949:

Dr. C. S. Hudson
Professor H. R. Kruyt
Professor H. S. Taylor
Professor A. W. K. Tiselius

The number of Honorary Fellows is now 29.

2. *Fellowship Statistics.* The Fellowship showed a net increase of 322 during 1949. At December 31st, there were 8195 names on the Register. 675 New Fellows were elected and 26 were reinstated. The Society has lost 60 Fellows by death, 210 by resignation, and 109 names were removed from the register. Of the total Fellowship, 4615 participated in the Joint Subscription Scheme sponsored by the Chemical Council.

3. *Joint Student Facilities.* During 1949, joint student facilities of the Chemical Society and the Society of Chemical Industry were granted by the Chemical Council to 17 persons.

4. *Honours.* The congratulations of the Society were conveyed to the following whose names appeared in the New Year and Birthday Honours Lists:

G.C.B.
Sir Henry Tizard

O.M.
Sir Robert Robinson

Knight Bachelor
Dr. W. G. Ogg
Dr. J. L. Simonsen

C.B.E.
Dr. J. R. Nicholls
Professor W. Wardlaw

The Council has also congratulated the following to whom awards have been made by the Royal Society:

Professor G. C. Hevesy, *Honorary Fellow*	Copley Medal
Professor R. A. Peters	Royal Medal
Professor A. R. Todd	Davy Medal

5. *Fellows who have completed* 70, 60, *and* 50 *years of Fellowship.* The congratulations of the Society have been conveyed personally by the President to Mr. William Stone, who completed 70 years of Fellowship on April 17th, 1949. Announcements have also been made at Ordinary Scientific Meetings, and have been published in the *Proceedings*, of the congratulations of the Society that have been sent to Fellows who during the year completed 60 and 50 years of Fellowship.

6. A list of Honorary Fellows and Fellows corrected to December 10th, 1948, was issued during the year, and copies * are available from the General Secretary.

* Price two shillings and sixpence.

II. PUBLICATIONS.

1. *Journal.* During the year 739 scientific communications were received, 13 were declined, and 6 withdrawn. The *Journal* contained 888 items, made up as follows (all the figures quoted in this Report include those for the two Supplementary Issues):

Papers (General, Physical, and Inorganic)	147
,, (Physical Organic)	125
,, (Organic)	530
Notes	68
Lectures and Addresses	6
Obituary Notices	11
Annual General Meeting	1

The Scientific Communications from overseas (141, including 9 jointly with British laboratories) increased both in total number and in proportion; contributions were received from: Australia (47), Austria (1), Canada (5), Egypt (25), France (6), Germany (1), Hungary (2), India (3), Irish Republic (6), Israel (4), New Zealand (15), Poland (2), South Africa (10), Spain (1), Sweden (3), and U.S.A. (10). Contributions from industrial laboratories totalled 101 (including 14 jointly with academic institutions), and those from industrial research organisations and Government laboratories totalled 42 (including 10 jointly with academic institutions).

The following are some figures relative to the growth of publication:

	1938.	1943.	1947.	1948.	1949.
Scientific communications received	507	208	523	548	739
Published	431	192	375	511	876

Of the 739 papers received during the whole of 1949, 426 were submitted during the last six months of the year. If this rate of submission continues, the *Journal* for 1950 will be about as large as that for 1949, although a considerable part of the 1949 *Journal* was devoted to overhauling arrears of publication.

The arrangements made in 1948 for an increased rate of publication in 1949 functioned satisfactorily; papers received in January 1949 began appearing in the June *Journal*, and by the end of the year there were no arrears of publication. In the December *Journal* the average time between receipt of a manuscript and its publication was about four to five months (plus about three weeks if the paper contained illustrations), and of this time two to three weeks were absorbed in the preparation of preprints. It is hoped that the time between the receipt of a paper and its publication can be further reduced by a few weeks as the arrangements for publication of these larger monthly issues are perfected; but no very great reduction can be effected under present conditions.

The progress in 1949 was possible only through the unfailing co-operation of the Society's printers, Messrs. Richard Clay & Co., Ltd.

2. *Annual Reports and Quarterly Reviews.* The *Annual Reports* for 1948 were distributed during September. It is hoped to distribute the *Annual Reports* for 1949 during July 1950.

Volume I (1947) of *Quarterly Reviews* was reprinted and became available during the year.

III. MEETINGS.

1. *Scientific Meetings.* The Society held 14 Meetings in London during 1949. These included 6 Lectures and 3 organised Discussions. At the other 5 Meetings, 12 papers were read and discussed.

109 Meetings arranged by Local Representatives on behalf of the Society, or in conjunction with other societies, were held outside London. In addition, Fellows were able to attend, under arrangements made locally, a number of meetings organised by other bodies.

Official Scientific Meetings of the Society were held at Newcastle on January 28th and Exeter on May 20th.

Details of all Meetings are given in Appendix A.

2. *Anniversary Meetings.* The 108th Annual General Meeting, The Presidential Address, and the Anniversary Dinner were held in London on March 31st. In conjunction with these meetings, a Discussion on "The Chemistry of the Heavy Elements," held at Oxford on March 28th—30th, and a Symposium on "The Use of Radioactive Tracers in Chemistry," held in London on April 1st, were organised by the Society and the Chemistry Division of the Atomic Energy Research Establishment.

A Report of the Annual General Meeting was published in the *Journal* for May. The papers presented at the meetings at Oxford and London were published in a Supplementary Issue of the *Journal*.

3. *Centenary Fund.* The income arising from the Centenary Fund has enabled the Society to invite a number of chemists from overseas to lecture and to take part in discussion meetings.

IV. LIBRARY.

The Annual Report of the Joint Library Committee for 1949 appears as Appendix B to this Report.

V. OTHER ACTIVITIES.

1. *Corday–Morgan Medal.* Rules governing the award of the Medal and Prize were approved by Council and published in the *Proceedings* for April.

The medal is to be awarded annually to the British Chemist, under thirty-six years of age who has, during the year for which the award is made, published the most meritorious contribution to experimental chemistry.

The award consists of a silver medal, designed by Mr. Percy Metcalfe, C.V.O., and a cash prize which will, it is expected, amount to not less than £150. Consideration will be given, at the end of 1950, to an award in respect of the year 1949.

2. *Flintoff Medal and Prize.* As stated elsewhere in the Report the bequest of the late Mr. R. J. Flintoff has been received and has been invested. The income will be accumulated until sufficient funds are available to institute the award.

3. *Copyright.* The Society has subscribed to a declaration, drawn up by the Royal Society and designed to make it easier for Scientists to obtain a single copy, for research purposes, of material which has appeared in the Society's Publications.

4. *Early Volumes of the Journal.* The Society has entered into an agreement for Volumes 1—23 of the *Journal*, 1848—1870, which are out of print, to be reprinted and published by Messrs. Butterworths (Scientific Publications), Ltd. The new edition is expected to be available in the autumn of 1950.

5. *Research Grants.* Grants from the Research Fund amounting to £775 2s. have been authorised for payment to 37 applicants.

6. *The Chemical Council and the Bureau of Abstracts.* The Reports for the year 1948 of the Chemical Council and of the Bureau of Abstracts have now been issued, and copies are available from the General Secretary.

7. *Accommodation.* Acute shortage of accommodation has continued to present serious difficulties to the Society. However, a new office has been formed, by conversion of part of the basement, and this has enabled the Society to restore to other bodies the privilege of holding scientific meetings in the Society's Meeting Room. Improved cloakroom facilities and a new central-heating system have been installed in the Society's apartments.

VI. ADMINISTRATION.

1. *Council.* At the Annual General Meeting on March 31st, 1949, the following were declared elected :

Vice-Presidents	Professor J. W. Cook, Professor W. Wardlaw.
Honorary Secretary	Professor H. Burton.
Ordinary Members of Council	Professor C. E. H. Bawn, Dr. F. S. Dainton, Dr. E. G. V. Percival, Dr. R. Spence, Professor M. Stacey, Dr. A. I. Vogel, Mr. J. D. Rose, Dr. J. Walker, Dr. W. A. Waters.

2. *Local Representatives.* The Council received with regret the resignation of a number of Local Representatives, and the following new appointments were made :

Edinburgh	Dr. Neil Campbell in place of Dr. E. G. V. Percival.
Glasgow.....	Dr. J. C. Speakman in place of Dr. J. D. Loudon.
Irish Republic	Dr. V. C. Barry in place of Professor T. S. Wheeler.
Manchester	Dr. M. A. T. Rogers in place of Dr. J. C. Withers.

Dr. D. O. Jordan has resumed his duties as Local Representative for Nottingham after twelve months' absence. The Council has also appointed Dr. M. U. S. Sultanbawa and Dr. M. I. D. Chughtai as the Society's first Local Representatives in the Dominions of Ceylon and Pakistan respectively.

3. *Editor.* The Council appointed Dr. R. S. Cahn as Editor of the Society's Publications as from March 1st, 1949.

VII. FINANCE.

1. *Investments.* The following alterations in the Society's Investments have been made during the year :

£259 14*s.* 9*d.* standing to the credit of Life Composition Fees in the General Purposes Account, invested in 3% British Transport Guaranteed Stock 1978/88.

£1,000, the W. H. Perkin Bequest, on the Publications Fund invested in 3% Southern Rhodesia Stock, 1971/73.

£150 on the Special Lectures Fund invested in 3% British Transport Guaranteed Stock, 1978/88.

£70 on the Faraday Lecture Fund invested in 3½% Conversion Stock, 1961, by the transfer of stock from the Staff Pensions Fund.

£4,500 on the Centenary Fund invested in 3% New Zealand Stock, 1973/77, and 2½% Savings Bonds, 1964/67.

£1,000 on the Robert John Flintoff Trust invested in 3% British Transport Guaranteed Stock, 1978/88, and 3½% Conversion Stock, 1961.

The following stocks on Special Reserve Fund were sold in order to provide funds for transfer to the General Purposes Account for meeting the cost of publications :

£2,400 2½% National War Bonds, 1949/51.
£3,700 2½% National War Bonds, 1952/54.

and £569 4*s.* 2*d.* 3½% Conversion Stock on Staff Pensions Fund (including the stock sold to the Faraday Lecture Fund) was realised.

2. *Contributions.* The Council gratefully acknowledge the following contributions towards the cost of the Society's publications :

£900 as a Supplementary grant for 1948 and £2,000 for 1949 from the Government Scientific Publications Grant-in-Aid, distributed by the Royal Society.

£1,333 6*s.* 8*d.* from the Chemical Council, representing part of the income received during the War and reserved for the publication of scientific papers accumulated during that period, and £1,000 as a grant for 1949.

A grant from the Ministry of Supply of half the cost of publication of the Supplementary issue of the *Journal* containing the papers discussed at the Symposium held at Oxford and in London in conjunction with the Anniversary Meetings.

The Council also gratefully acknowledge donations from Dr. A. F. Campbell, Dr. D. Holmes, Pharmaceutical and Allied Chemicals Disposals, Ltd., and others, as well as contributions received for the Centenary Fund under deeds of covenant.

3. *Library.* The Council records its thanks for a contribution of £200 received through the Royal Society from the Government Scientific Publications Grant-in-Aid, towards the cost of capital expenditure on the Library, and for the following contributions, on a membership basis, received through the Chemical Council towards the maintenance costs of the Library:

	£	s.	d.
The Royal Institute of Chemistry	1188	19	4
The Society of Chemical Industry	638	1	0
The Faraday Society	132	2	2
The Society of Public Analysts and Other Analytical Chemists	101	3	9
The Biochemical Society	132	2	2

The Chemical Society's share of the maintenance costs of the Library amounted to £618 7*s.* 6*d.*, and in addition the Society has contributed over £900 towards the purchase of new books and other Capital expenditure on the Library.

Contributions towards the maintenance expenses have also been received from other sources as follows:

	£	s.	d.
Association of British Chemical Manufacturers	100	0	0
Institute of Brewing	50	0	0
Genatosan, Ltd.	25	0	0
Society of Dyers and Colourists	10	10	0

4. *Increased Prices of Publications.* The increasing cost of producing the Society's publications has compelled the Council to increase during the year, to £6 per annum, the price at which the *Journal* is sold to non-Fellows; the *Annual Reports on the Progress of Chemistry* was increased to £1 5*s.* 0*d.* per volume, and the *Quarterly Reviews* to £1 10*s.* 0*d.* per annum.

The Council also found it necessary to ask Fellows to bear a proportion of the increased costs, and the prices of the publications on the schedule were increased as from January 1st, 1950.

5. *Advertisements.* During the year, Messrs. Walter Judd, Ltd., were appointed the Society's agents for procuring advertisements for the Society's publications.

VIII. REPRESENTATION ON OTHER BODIES.

The Society's representatives at December 31st, 1949 were as follows:

Association of British Chemical Manufacturers:

Joint Technical Committee on Patents: Dr. J. T. Hewitt.

Barker Committee:

Formed to support the publication of the Barker Index of the characteristic angles of crystalline compounds: Dr. G. M. Bennett.

Bristol University Court:

Sir Norman Haworth.

British National Committee for Chemistry:

Sir Norman Haworth, Sir Cyril Hinshelwood, Professor M. Stacey.

British National Committee for Crystallography:

Dr. G. M. Bennett.

British Standards Institution. Technical Committees :

M/1. Units and Technical Data : Professor C. W. Davies.
M/4. Letter Symbols : Professor C. W. Davies.
C/17. Viscosity : Dr. A. E. Dunstan.
C/18. Chemical Symbols and Abbreviations : Professor C. W. Davies.
C/34. Standardisation of pH Scale : Professor H. T. S. Britton.
CHE/36. Chemicals for Electroplating : Dr. U. R. Evans.
DAC/-. Standards for Dairying Chemistry : Mr. Eric Voelker.
LBC/-. Scientific Glassware and Related Laboratory Apparatus : Dr. G. R. Davies.
LBC/2/1. Ubbelohde Apparatus : Dr. G. R. Davies.
LBC/5. Hydrometers : Mr. R. Sutcliffe.
LBC/6. Standard Distillation Apparatus : Mr. R. Sutcliffe.
LBC/11. Microchemical Apparatus : Dr. H. D. K. Drew, Professor H. B. Nisbet.
LGE/19. Colour Terminology : Dr. F. M. Hamer.
PCC/1. Nomenclature for Insecticides : Dr. R. L. Wain.

Bureau of Abstracts.

Directors and Members : Dr. G. M. Bennett, Mr. F. P. Dunn, Dr. E. B. Hughes, Dr. E. H. Rodd.

Members : Mr. R. P. Bell, Professor H. V. A. Briscoe, Dr. A. H. Cook, Professor W. Wardlaw.

Chemical Council :

The Treasurer, Sir Ian Heilbron, Professor D. H. Hey, Dr. R. P. Linstead.

City and Guilds of London Institute :

The President.

Faraday Society. Colloid and Biophysics Committee :

Dr. P. Johnson.

Joint Library Committee :

Dr. A. H. Cook, Dr. C. H. Desch, Mr. M. B. Donald, Dr. F. Fairbrother, Dr. P. Haas, Dr. T. A. Henry, Dr. J. R. I. Hepburn, Professor D. H. Hey, Professor E. D. Hughes, Dr. Harold King, Professor G. A. R. Kon, Dr. H. N. Rydon, Dr. F. C. Tompkins, Professor E. E. Turner.

Lawes Agricultural Trust :

Committee of Management : Sir Norman Haworth.

Parliamentary and Scientific Committee :

The President, Professor D. H. Hey.

Regional Council for Further Education for the South-West :

Chemistry and Chemical Technology Committee : Professor W. E. Garner.

Royal Society.

Joint Standing Committee for Symbols and Abbreviations : Mr. R. P. Bell, Professor C. W. Davies.

Scientific Societies Accommodation Committee :

The President.

Yorkshire Council for Further Education :

Advisory Committee for Chemistry in South and East Yorkshire : Professor R. D. Haworth, Professor Brynmor Jones.

IX. ACKNOWLEDGMENTS.

The Council expresses its cordial thanks to the many Fellows who have served the Society in various ways during the year, including Members of Committees, Referees of papers submitted for publication, Contributors to the *Annual Reports* and *Quarterly Reviews*, Local Representatives, and those who have given Lectures and opened Discussions.

APPENDIX A.

MEETINGS HELD DURING 1949.

IN LONDON.

Unless otherwise stated all meetings were held in the Rooms of the Society at Burlington House.

January 20th, at the Royal Institution, *Tilden Lecture*, "Three- and Four-membered Heterocyclic Rings", by Professor F. E. King; February 3rd, *Johannes Nicolaus Brønsted Memorial Lecture*, by Mr. R. P. Bell; February 17th, at Imperial College of Science and Technology, *Centenary Lecture*, "Recent Developments in the Chemistry of Macrocyclic Compounds", by Professor Dr. V. Prelog; March 3rd, *Meeting* for reading papers; March 17th, *Discussion*, "Aspects of Heterogeneous Catalysis", arranged by Dr. R. Holroyd. Part I, "Theoretical Basis", by Mr. D. A. Dowden; Part II, "Hydrogenation by Binary Alloys", by Dr. P. W. Reynolds; April 1st, at the Institution of Civil Engineers, *Discussion*, "The Use of Radioactive Tracers in Chemistry"; April 28th, *Meeting* for reading papers; May 12th, at the Royal Institution, *Centenary Lecture*, "The Chemistry and Biochemistry of some Mammalian Secretions and Excretions", by Dr. E. Lederer; May 26th, *Meeting* for reading papers; October 20th, at Imperial College of Science and Technology, *Tilden Lecture*, "Acetylene and Acetylenic Compounds in Organic Synthesis", by Professor E. R. H. Jones; November 3rd, *Meeting* for reading papers; November 17th, at the Institution of Mechanical Engineers, *Centenary Lecture*, "Radiation-induced Polymerisation", by Dr. M. Magat; November 30th, at the Royal Institution, *Symposium*, "Fluorine Chemistry", arranged by Professor H. J. Emeléus; December 15th, *Meeting* for reading papers.

OUTSIDE LONDON.

Aberdeen. Joint meetings with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry, in the Chemistry Department, Marischal College; January 14th, *Lecture*, "Sulphide Precipitation and the Law of Mass Action", by Mr. R. Belcher; January 27th, *Lecture*, "Application of Dyestuffs to Materials other than Textiles", by Mr. J. G. Grundy; February 25th, *Lecture*, "Some Factors influencing the Strengths of Acids and Bases", by Professor D. H. Everett; March 10th, *Lecture*, "Recent Advances in Seaweed Technology", by Dr. F. N. Woodward; October 27th, *Lecture*, "Peat", by Dr. G. K. Fraser; November 11th, *Tilden Lecture*, "Acetylene and Acetylenic Compounds in Organic Synthesis", by Professor E. R. H. Jones; December 2nd, *Lecture*, "Some Aspects of the Work at Rothamsted", by Sir William G. Ogg; December 12th, *Lecture*, "Some Recent Advances in the Chemistry of Fluorine Compounds", by Professor H. J. Emeléus.

Birmingham. At the University (joint meetings with the University Chemical Society): March 18th, *Lecture*, "Some Aspects of Stereochemistry", by Dr. F. G. Mann; October 21st, *Lecture*, "The Oxidation of Aldehydes in Solution", by Professor C. E. H. Bawn; December 2nd, *Lecture*, "Chemical Constitution and Biological Activity", by Dr. W. A. Sexton.

Bristol. At the University (joint meetings with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry): February 10th, *Lecture*, "The

Stability of Emulsions", by Dr. A. S. C. Lawrence; November 3rd, *Lecture*, "What is a Chemical Bond?", by Professor C. A. Coulson.

Edinburgh. January 13th, at the North British Station Hotel (joint meeting with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry), *Lecture*, "Amphipathic Behaviour in Colloid Systems", by Dr. T. R. Bolam; February 8th, at the University (joint meeting with the local sections of the Royal Institute of Chemistry, the Society of Chemical Industry and the University Chemical Society), *Lecture*, "Some Recent Advances in the Chemistry of Natural Products", by Professor R. D. Haworth; at the North British Station Hotel (joint meetings with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry): February 24th, *Lecture*, "Analytical Chemistry, Chemical Analysis, and the Analyst", by Mr. R. C. Chirnside; March 17th, *Lecture*, "Recent Trends in the Industrial Utilisation of Agricultural Products in North America", by Dr. F. N. Woodward; October 20th, *Lecture*, "The Cow—Mankind's Benefactress", by Mr. E. B. Anderson; November 17th, *Lecture*, "Radical Chemistry applied to Problems in the Hydrocarbon, Drying Oil, and Rubber Fields", by Dr. E. H. Farmer; December 8th, at the Y.M.C.A. Hall (joint meeting with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry), Scientific Film display.

Exeter. At Washington Singer Laboratories: May 6th and 7th (joint meetings with British Rheologists' Club), *Discussion*, "Suspensions and Sedimentation"; May 20th, Official Meeting of the Society and *Lecture*, "A New Approach to the Synthesis of Azoles and Purines", by Sir Ian Heilbron; October 14th (joint meeting with University College Scientific Society), *Lecture*, "Diffraction of Neutrons by Crystals", by Dr. Kathleen Lonsdale; November 25th (joint meeting with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry), *Lecture*, "Corrosion Inhibitors", by Dr. U. R. Evans; December 2nd (joint meeting with University College Scientific Society), *Lecture*, "Catalysis and the Surface Levels of Copper Oxide", by Professor W. E. Garner.

Glasgow. February 21st, at the Royal Technical College, Annual General Meeting of the Local Section and *Centenary Lecture*, "Recent Developments in the Chemistry of Macrocyclic Compounds", by Professor V. Prelog; at the University: March 11th, *Lecture*, "The Head-to-tail Isoprene Rule and its Limitations in Terpene Chemistry", by Professor G. R. Clemo; October 28th (joint meeting with the Alchemists' Club and the Andersonian Chemical Society), *Lecture*, "The Art of making Sulphate of Ammonia", by Dr. M. P. Applebey; November 25th, *Lecture*, "Modern Theories of Chemical Valency", by Sir John Lennard-Jones.

Hull. At University College: February 24th (joint meeting with the local section of the Royal Institute of Chemistry and University College Scientific Society), *Lecture*, "The Nature of Scientific Convictions", by Professor M. Polanyi; (joint meetings with University College Scientific Society): April 28th, *Lecture*, "Some Recent Developments in the Chemistry of Natural Products", by Professor R. D. Haworth; October 20th, *Lecture*, "The Mechanism of Drug Action", by Professor A. R. Todd; November 10th, *Lecture*, "Surface Films", by Professor N. K. Adam.

Irish Republic. At University College, Dublin (joint meetings with University College Chemical Society and the Werner Society): February 28th, *Lecture*, "Researches on the Chemistry of the Algæ", by Professor T. Dillon; March 7th, *Lecture*, "The Chemistry of Reductone and its Bearing on Sulphanilamide Action", by Professor W. Cocker; at Trinity College, Dublin, March 14th, *Lecture*, "The Development of the Periodic Table", by Professor T. S. Wheeler; May 6th (joint meeting with the Werner Society), *Lecture*, "Recent Progress in the Chemistry of Pectin and Hemicelluloses", by Professor E. L. Hirst; May 16th, *Centenary Lecture*, "The Chemistry and Biochemistry of some Mammalian Secretions and Excretions", by Dr. E. Lederer; May 27th (joint meeting with the Werner Society), *Lecture*, "A Chapter in Inorganic Stereochemistry", by Professor W. Wardlaw; October 21st (joint meeting with the Werner Society), *Lecture*, "Methods of Biological Assay", by Mr. A. L. Bacharach; November 2nd, at University College, Dublin, *Lecture*, "Some Biologically Active Phenazine Derivatives", by Mr. J. G. Belton; November 25th, at Trinity College, Dublin (joint meeting with the Werner Society),

Lecture, "The Head-to-tail Isoprene Rule and its bearing on Terpene Chemistry", by Professor G. R. Clemo.

Leeds. At the University: March 15th (joint meeting with the University Chemical Society), Debate followed by *Lecture*, "Structural Relationships amongst the Polysaccharides", by Professor E. L. Hirst; May 20th, *Centenary Lecture*, "The Chemistry and Biochemistry of Some Mammalian Secretions and Excretions", by Dr. E. Lederer.

Liverpool. At the University: February 10th, *Lecture*, "Recent Advances in the Physical Chemistry of High Polymers", by Dr. G. Gee; February 24th, *Centenary Lecture*, "Some Recent Advances in the Chemistry of Macrocyclic Compounds", by Professor Dr. V. Prelog; October 27th, *Lecture*, "Editing for the Chemical Society", by Dr. R. S. Cahn; November 6th, *Centenary Lecture*, "Radiation-induced Polymerisation", by Dr. M. Magat; December 15th, *Lecture*, "The Biological Oxidation of certain Aromatic Compounds with Special Reference to the Bacterial Cleavage of the Benzene Ring", by Dr. W. C. Evans.

Manchester. January 7th, at the Engineer's Club (joint meeting with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry), *Lecture*, "Production of Acetylene from Hydrocarbons", by Dr. H. Steiner; February 22nd, at the University, *Centenary Lecture*, "Recent Developments in the Chemistry of Macrocyclic Compounds", by Professor Dr. V. Prelog; February 24th, at the Engineers' Club (joint meeting with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry), *Lecture*, "Some Recent Developments in Inorganic Chromatography", by Dr. R. P. Linstead; March 10th, at the University, *Meeting* for reading papers; March 24th, at the Engineers' Club (joint meeting with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry), *Lecture*, "The Chemistry of the Deoxy-sugars", by Professor M. Stacey; October 20th, at the University, *Meeting* for reading papers; November 9th, at the University (joint meeting with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry), *Symposium*, "Some Chemical Aspects of Atomic Energy"; December 2nd, at the Gas Show Rooms (joint meeting with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry), *Lecture*, "Some Studies of Oxidation–Reduction Reactions", by Professor M. G. Evans.

Newcastle and Durham. At King's College, Newcastle-on-Tyne: January 14th, *Bedson Club Lecture*, "Chemistry and Atomic Energy", by Dr. R. Spence; January 28th, Official Meeting of the Society and *Tilden Lecture*, "Three- and Four-membered Heterocyclic Rings", by Professor F. E. King; February 11th, *Bedson Club Lecture*, "Partition Chromatography", by Dr. A. J. Martin; March 4th, *Meeting* for reading papers; May 13th, *Bedson Club Lecture*, "The Kinetics of Oxidation Reactions in the Gaseous Phase", by Sir Cyril Hinshelwood; May 19th, *Centenary Lecture*, "The Chemistry and Biochemistry of Some Mammalian Secretions and Excretions", by Dr. E. Lederer; November 25th, *Meeting* for reading papers. Fellows were invited to all meetings of the Bedson Club as well as those organised by other bodies.

Northern Ireland. At Belfast (joint meetings with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry): January 21st, *Lecture*, "The Flax Wet Spinning Frame as a Source of Catalytic Damage in Bleaching", by Dr. W. Honneyman; February 9th, *Lecture*, "Some Problems of the Sensitiveness of Explosives", by Professor A. R. Ubbelohde; March 2nd, *Lecture*, "The Future of Synthetic Detergents in Relation to the Petroleum Chemical Industry", by Mr. A. K. Simcox; May 10th (joint meeting with the Microchemical Group of the Society of Public Analysts and the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry), *Meeting* for reading of papers; May 17th, *Centenary Lecture*, "The Chemistry and Biochemistry of Some Mammalian Secretions and Excretions", by Dr. E. Lederer.

North Wales. February 17th, at University College of North Wales, Bangor (joint meeting with the University College of North Wales and the University of Liverpool Chemical Societies), *Lecture*, "Corrosion: The Study of Surface Reactions on Metals", by Dr. W. H. J. Vernon; (joint meetings with University College of North Wales Chemical Society): March 3rd, at the Edward Davies Chemical Laboratories, Aberystwyth, *Lecture*,

" The Liquid State ", by Dr. A. E. Moelwyn-Hughes; at University College of North Wales: May 5th, *Lecture*, " Problems in the Chemistry of the Pectin and Hemicelluloses ", by Professor E. L. Hirst; November 24th, *Lecture*, " A New Type of Aromatic Compound ", by Professor W. Baker.

Nottingham. At the University (joint meetings with the University Chemical Society): January 27th, *Lecture*, " Some Aspects of Structural Inorganic Chemistry ", by Dr. A. F. Wells; February 24th, *Lecture*, " The Shape of the Chemical Bond ", by Professor C. A. Coulson; March 10th, *Lecture*, " Some Metabolic Products of Moulds ", by Professor A. Robertson; October 20th, *Lecture*, " The Scattering of Light by Solutions ", by Dr. E. J. Bowen; November 10th, *Lecture*, " Organic Compounds of Fluorine ", by Professor M. Stacey; December 1st, *Meeting* for reading papers.

Oxford. Fellows were invited to the following *Alembic Club Lectures* held at the Physical Chemistry Laboratory: January 24th, *Lecture*, " Some Remarks on the Periodic Table ", by Professor N. V. Sidgwick; February 7th, *Lecture*, " Localised and Non-localised Bonds ", by Professor C. A. Coulson; February 28th (joint meeting with the local section of the Royal Institute of Chemistry), *Lecture*, " Research and Productivity in Industry," by Mr. C. S. Robinson; May 9th, *Lecture*, " π-Electrons in Organic Chemistry ", by Dr. M. J. S. Dewar; May 17th, *Lecture*, " The Liquid State ", by Dr. E. A. Moelwyn-Hughes; October 17th, *Lecture*, " Compounds of the Inert Gases ", by Mr. H. M. Powell; October 31st, *Lecture*, " Micro-wave Spectroscopy ", by Professor E. Bright Wilson; November 21st, *Lecture*, " Synthesis of Nucleotides ", by Professor A. R. Todd.

St. Andrews and Dundee. February 10th, at University College, Dundee [joint meeting with the local sections of the Royal Institute of Chemistry, the Society of Chemical Industry and in conjunction with the British Association (Dundee) Trust], *Lecture*, " Soil Fertility ", by Dr. W. G. Ogg; February 25th, at United College, St. Andrews (joint meeting with the local section of the Royal Institute of Chemistry and the University Chemical Society), *Lecture*, " Free Radicals and Hydrocarbon Chemistry ", by Professor C. E. H. Bawn; April 7th, at University College, Dundee, *Lecture*, " Some Recent Advances in Surface Chemistry ", by Dr. A. E. Alexander; April 29th, at United College, St. Andrews, *Lecture*, " Recent Developments in the Chemistry of Glutamic Acid and its Compounds ", by Professor F. E. King; at University College, Dundee: October 21st, *Lecture*, " Chemical Reactions induced by Nuclear Radiations ", by Dr. F. S. Dainton; October 27th, *Lecture*, " The Chemistry of Metallic Oxides ", by Dr. J. S. Anderson.

Sheffield. At the University (joint meetings with the University Chemical Society): February 17th, *Lecture*, " Hydrogen Peroxide as an Ionising Solvent ", by Professor W. F. K. Wynne-Jones; March 3rd, *Lecture*, " The Chemistry of Colchicine ", by Professor J. W. Cook; November 3rd, *Lecture*, " Some Aspects of the Organic Chemistry of Fluorine ", by Dr. C. W. Suckling; December 1st, *Lecture*, " Some Oxidations involving Free Radicals ", by Dr. W. A. Waters.

Southampton. January 28th, at University College (joint meeting with the University College Chemical Society), *Lecture*, " Some Aspects of Recent Work at the Chemical Research Laboratory, Teddington ", by Dr. R. P. Linstead; February 2nd, at the Municipal College, Portsmouth (joint meeting with the Mid-Southern Counties Section of the Royal Institute of Chemistry, the London Section of the Society of Chemical Industry and the Portsmouth and District Chemical Society), *Lecture*, " Food Science in Evolution ", by Dr. L. H. Lampitt; at University College: May 6th (joint meeting with the University College Chemical Society), *Lecture*, " Some Aspects of Aromatic Substitution ", by Professor Brynmor Jones; October 21st (joint meeting with the Mid-Southern Counties Section of the Royal Institute of Chemistry and the University College Chemical Society), *Lecture*, " Medical Aspects of Radiation Chemistry ", by Dr. Edson; November 25th (joint meeting with the University College Chemical Society), *Lecture*, " Macro-molecular Studies with the Electron-microscope ", by Professor W. T. Astbury.

South Wales. At University College, Swansea: January 21st, *Lecture*, " The Oxidation of Phenols ", by Professor R. D. Haworth; (joint meetings with University College of Swansea Students' Chemical Society): February 3rd, *Lecture*, " The Friction and

Lubrication of Metal Surfaces", by Dr. F. B. Bowden; March 11th, *Lecture*, "The Function of Sulphuric Acid in Aromatic Nitration", by Dr. G. M. Bennett; October 27th, at University College, Cardiff, *Lecture*, "Aromatic Nitration", by Professor C. K. Ingold; at University College, Swansea: October 28th (joint meeting with the local section of the Royal Institute of Chemistry and University College of Swansea Students' Chemical Society), *Lecture*, "Aromatic Nitration", by Professor C. K. Ingold; November 18th (joint meeting with University College of Swansea Students' Chemical Society), *Lecture*, "The Formation and the Reactions of Free Radicals in Solution", by Professor M. G. Evans; at University College, Cardiff: November 30th, *Lecture*, "Some Recent Advances in the Physical Chemistry of High Polymers", by Dr. G. Gee.

APPENDIX B.

ANNUAL REPORT OF THE JOINT LIBRARY COMMITTEE FOR THE YEAR 1949.

Problems arising from war-time activities, and from re-adjustments in the chemical industry immediately after the war, were reflected in the abnormal increase in the number of readers using the Library and in the number of books borrowed. This phase having passed, it is not surprising that there were decreases in the number of attendances and of books borrowed during the year 1949. The more prolonged use made of the Library on the average by individual readers, however, together with the more complex nature of the enquiries received, suggest that the Library is utilised for problems of a more fundamental character than ever. A substantial increase in the number of books issued by post makes it clear that the value of the Library is becoming more fully appreciated in the provinces.

The photostat service is still meeting a real need; during the year, the number of printed pages copied was 5018, an increase of 413 on the previous year. There were 1985 telephone enquiries, an increase of 221 over the figures for 1948. The number of books added to the Library was 319, of which 71 were presented. There were 573 volumes of periodicals added and 224 pamphlets. The total number of volumes in the Library is now 50,679, of which 15,373 are books and 35,306 volumes of periodicals.

	Attendances.	Books borrowed.	Books added.	Volumes of periodicals added.	Pamphlets added.
1949	10,778	8926 (4177 by post)	319	573	224
1948	11,547	9741 (3569 by post)	282	583	187

It has been found possible to waive the Regulation requiring the registration of Library books sent through the post to addresses in Great Britain, and certain other Library Regulations have been simplified.

It gives the Committee much pleasure to record its sincere thanks to those authors and publishers who have courteously presented copies of newly published works to the Library, and also to Fellows and others who have enriched the Society's historical collection by the gift of copies of earlier publications.

INCOME AND EXPENDITURE GENERAL PURPOSES ACCOUNT FOR THE YEAR ENDED 31ST DECEMBER, 1949.

1948 £ s. d.	1948 £ s. d.	*Income.*	1949 £ s. d.	1949 £ s. d.
	125 1 9	To Life Composition Fees (£60 15s. 9d.), one-third as Income		23 5 0
		„ Annual Subscriptions :		
		Single-body Fellows—		
2915 0 11		Received in advance, on account of 1949	4260 2 4	
6779 7 6		Received during 1949 on account of 1949	5806 19 8	
226 1 9		Received during 1949 on account of 1948 and previous years	245 16 8	
		Joint Fellows—		
2768 12 7		Received in advance, on account of 1949	350 10 2	
9024 17 10		Received during 1949 on account of 1949	11,374 19 3	
148 13 6		Received during 1949 on account of 1948 and previous years	158 13 6	
21,863 13 0			22,296 19 8	
— — —		*Add* Excess amount provided in 1948 for adjustment with Society of Chemical Industry	531 0 0	
21,863 13 0			22,827 19 8	
1000 0 0		*Less* Liability to the Society of Chemical Industry to adjust cost of publications supplied to Joint Members	199 0 0	
20,863 13 0			22,628 19 8	
350 0 0		*Less* Amount included in last year's Income, being valuation of Arrears as per last Balance Sheet	300 0 0	
20,513 13 0			22,328 19 8	
300 0 0		*Add* Arrears to date estimated to realise as per Balance Sheet	300 0 0	
	20,783 13 0			22,628 19 8
	341 6 7	„ Dividends on Investments		304 0 11
	289 14 5	„ Income Tax recovered		300 9 10
	102 13 2	„ Donations		91 18 2
	100 0 0	„ Legacy—Hugh Main		— — —
	134 4 5	„ Miscellaneous Receipts		101 9 5
	1033 8 10	„ Balance, being Excess of Expenditure over Income, carried to Balance Sheet		111 4 5
	£23,077 0 11			£23,651 7 5

1948 £ s. d.	1948 £ s. d.	*Expenditure.*	1949 £ s. d.	1949 £ s. d.
		By Administration Expenses :		
3991 2 5		Office Salaries and Wages	4204 9 1	
408 3 7		Superannuation	461 19 10	
1359 11 6		House Expenses, etc.	1126 11 0	
126 0 0		Accountants' Charges	117 12 0	
932 6 4		Printing, Stationery, and Office Expenses	617 9 2	
291 12 7		Postages	290 10 3	
107 7 2		Furniture	204 10 0	
313 15 6		Miscellaneous	268 9 1	
9410 2 1			7429 6 7	
		Less Transfer to Publications and Library :		
1090 10 9		Journal	— — —	
208 3 10		Annual Reports	— — —	
208 3 10		Quarterly Reviews	— — —	
244 14 11		Library Account	— — —	
	7655 8 10			7429 6 7
	636 1 9	„ Expenses on Account of Conjoint Chemical Office (including salaries for 1949)		1400 0 0
	233 0 6	„ Expenses of Meetings		411 16 6
	21 10 0	„ Donations		31 10 0
	13,600 15 9	„ Balance of Expenditure on Publications to Publications Account		11,810 4 4
		„ Contribution to Library Account :		
473 11 11		For Fittings, Furniture, Books, Periodicals, and Binding	943 6 9	
547 17 10		Proportion of Maintenance	616 7 6	
	1021 9 9			1561 14 3
	— — —	„ Transfer to Staff Pensions Fund		300 0 0
	255 10 8	„ Expenses of Local Representatives		296 17 6
	11 13 0	„ Legal Charges		21 10 0
	292 14 1	„ Travelling Expenses of Members of Council		340 16 9
	64 11 7	„ Loss on Exchange (Australia)		94 11 6
	£23,077 0 11			£23,651 7 5

INCOME AND EXPENDITURE ACCOUNTS OF OTHER FUNDS FOR THE YEAR ENDED 31ST DECEMBER, 1949.

PUBLICATIONS.

1948			*Income.*	1949		
£ s. d.	£ s. d.			£ s. d.	£ s. d.	
6320 3 11			To Publication Sales (including back numbers):			
1296 10 4			Journals and Proceedings	8705 5 6		
380 17 11			Annual Reports on Progress of Chemistry	1447 10 4		
670 6 11			Quarterly Reviews	1504 10 5		
290 0 5			Authors' Extra Reprints	1766 16 6		
54 1 9			Abstracts (Back Nos. only 1944 and earlier)	392 14 2		
	9092 13 5		Other Publications	12 3 5		
					13,777 9 10	
1611 17 8			„ Net Proceeds of Advertisements:			
— — —			Journal	784 13 7		
71 17 9			Quarterly Reviews	49 5 11		
	1083 14 2		Annual Reports	73 16 11		
					906 15 6	
	2500 0 0		„ Donations:			
			Chemical Council		2431 6 8	
			„ Government Publications Grant (through the Royal Society):			
— — —			Balance 1948	900 0 0		
800 0 0			Grant 1949	3000 0 0		
	900 0 0				3900 0 0	
	— — —		„ Cost of publishing Tilden Lectures: Transfer from the Tilden Lecture Fund ...		28 4 0	
	— — —		„ Cost of publishing Centenary Lectures: Transfer from the Centenary Fund		80 0 0	
	— — —		„ Donations		736 16 9	
	996 7 7		„ Dividends on Investments		196 3 6	
	107 4 0		„ Income Tax recovered		133 5 6	
	2100 0 0		„ Transfer from Special Reserve Fund ...		9000 0 0	
	12 0		„ Miscellaneous Receipts		6 12 7	
	12,690 15 9		„ Transfer from General Purposes Account (the balance of expenditure on publications)		11,810 4 4	
	£29,081 6 9				£41,875 18 0	

1948			*Expenditure.*	1949		
£ s. d.	£ s. d.			£ s. d.	£ s. d.	
			By Expenses on account of Journal:			
2183 16 6			Salaries and Wages	2631 11 11		
104 18 1			Superannuation	335 6 5		
13,706 7 7			Printing and Paper	11,088 19 6		
2235 9 1			Binding and Distribution	2050 1 6		
1346 2 6			Authors' Reprints	2048 12 3		
60 0 0			Indexing	100 0 0		
78 10 4			Furniture	62 0 9		
— — —			Office Printing and Stationery	134 0 6		
70 17 8			Editorial Postages	129 4 5		
140 8 11			Miscellaneous	302 6 2		
1099 10 6			Overhead Expense (proportion) ...	— — —		
	19,997 1 6				21,982 6 5	
	6300 0 0		„ Contributions to Bureau of Abstracts: Grants		6360 0 0	
	63 1 11		„ Distribution of Abstracts (Back Nos. only 1944 and earlier)		— — —	
	1020 11 11		„ Annual Reports on the Progress of Chemistry		2164 16 5	
	1791 9 6		„ Quarterly Reviews		3467 14 11	
	£29,081 6 9				£41,975 18 0	

INCOME AND EXPENDITURE ACCOUNTS OF OTHER FUNDS FOR THE YEAR ENDED 31ST DECEMBER, 1949.

LIBRARY.

Income.

1948 £ s. d.	£ s. d.		1949 £ s. d.	£ s. d.
		To Contribution for Fittings, Furniture, Books, Periodicals, and Binding:		
473 11 11		Transfer from General Purposes Account ...	943 6 9	
80 2 7		Transfer from Special Reserve Fund (deferred expenditure)	— — —	
— — —				
100 0 0		„ Government Grant (through the Royal Society)	200 0 0	
	653 14 6	„ Legacy—G. McGowan	— — —	1143 6 9
		„ Contributions towards maintenance:		
		Through the Chemical Council:		
247 17 10		Chemical Society (transfer from General Purposes Account)	618 7 6	
1083 8 10		Royal Institute of Chemistry	1188 19 4	
566 6 6		Society of Chemical Industry	638 1 0	
117 1 0		Faraday Society	132 2 2	
		Society of Public Analysts and other Analytical Chemists	101 3 9	
117 1 0		Biochemical Society	132 2 2	
630 7 8		From the Chemical Council	825 6 7	
	3060 15 11			3436 2 6
		„ Contributions, etc., received from other sources towards maintenance:		
		Association of British Chemical Manufacturers	100 0 0	
100 0 0		Institute of Brewing	50 0 0	
50 0 0		Society of Dyers and Colourists	10 10 0	
10 10 0		Miscellaneous receipts	60 10 5	
56 12 5				
	217 3 5			221 0 5
	£3931 13 10			£5000 9 5

Expenditure.

1948 £ s. d.	£ s. d.		1949 £ s. d.	£ s. d.
		By Capital and Extraordinary Expenditure:		
604 6 6		Books and Periodicals*	870 10 6	
— — —		Furniture	34 0 9	
19 8 0		Binding	238 9 6	
	622 14 6			1143 6 9
		„ Maintenance:		
2616 10 4		Salaries and Wages	3049 8 7	
269 19 2		Superannuation of Library Staff	277 2 10	
49 16 4		Postages	66 11 4	
— — —		Home Expenses, etc.	199 0 6	
— — —		Office Expenses and Stationery	121 15 9	
26 19 7		Miscellaneous Expenses	134 2 11	
264 14 11		Overhead Expenses (proportion)	— — —	
	2277 13 4			3847 2 11
	£2931 13 10			£5000 9 5

* Other than those received in exchange.

INCOME AND EXPENDITURE ACCOUNTS OF OTHER FUNDS FOR THE YEAR ENDED 31ST DECEMBER, 1949.

SPECIAL RESERVE FUND.

1948	Income.	1949	1948	Expenditure.	1949
£ s. d.		£ s. d.	£ s. d.		£ s. d.
315 11 5	To Dividends on Investments	330 1 7	319 19 10	By Expenses on Change of Investments	— — —
16 4 4	„ Interest on Deposit	14 2 9		„ Balance, being Excess of Income over Expenditure, carried to Balance	
84 2 2	„ Income Tax recovered	97 1 1	100 18 1	Sheet	481 8 8
£415 17 11		£481 8 8	£415 17 11		£481 8 8

RESEARCH FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
146 4 6	To Dividends on Investments	150 15 0	867 0 0	By Grants awarded	773 3 0
260 16 7	„ Income Tax recovered	206 7 7	21 0 0	„ Honorarium, Hugo Müller Lecture	— — —
20 1 0	„ Repayment of Grants	25 12 8	— — —	„ do., Longstaff Medallist	20 0 0
5 10 0	„ Interest on Deposit	5 7 1	5 0 2	„ The Longstaff Medal	— — —
17 10 0	„ Sale of Apparatus	2 10 0	15 19 6	„ Miscellaneous Expenses	34 19 4
20 0 0	„ Grants not claimed	70 0 0			
	„ Balance, being Excess of Expenditure over Income, carried to Balance				
179 3 4	Sheet	111 13 0			
£620 15 10		£630 1 4	£908 19 10		£630 1 4

SPECIAL PUBLICATIONS FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
23 12 10	To Sales of Publications	55 1 2	459 2 9	By Cost of Publications	602 6 11
50 1 10	„ Dividend on Investments	59 9 2	2 9 0	„ Miscellaneous Expenses	6 6 9
— — —	„ Income Tax recovered	20 0 4			
16 1 2	„ Interest on Deposit	16 16 9			
	„ Balance, being Excess of Expenditure over Income, carried to Balance				
330 16 10	Sheet	382 1 1			
£474 11 9		£608 18 8	£464 11 9		£608 18 8

INCOME AND EXPENDITURE ACCOUNTS OF OTHER FUNDS FOR THE YEAR ENDED 31ST DECEMBER, 1949.

STAFF PENSIONS FUND.

1948	*Income.*	1949	1948	*Expenditure.*	1949
£ s. d.		£ s. d.	£ s. d.		£ s. d.
— — —	To Transfer from General Account	500 0 0	840 0 0	By Pensions paid	865 0 0
79 4 11	„ Dividends on Investments	91 2 7	— — —	„ Miscellaneous Expenses	6 14 8
22 12 6	„ Income Tax recovered	11 14 9			
14 7 4	„ Interest on Deposit	11 9 1			
	„ Balance, being Excess of Expenditure over Income, carried to Balance Sheet	337 7 10			
723 15 5					
£840 0 0		£971 14 8	£840 0 0		£971 14 8

THE EDWARD FRANK HARRISON MEMORIAL TRUST FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
— — —		— — —	— — —		— — —
28 5 0	To Dividends on Investments	26 14 10	150 0 0	By Harrison Prize	9 6 10
22 11 10	„ Income Tax recovered	20 7 0	2 7 0	„ Miscellaneous Expenses	
1 10	„ Interest on Deposit	— — —		„ Balance, being Excess of Income over Expenditure, carried to Balance Sheet	44 10 0
	„ Balance, being Excess of Expenditure over Income, carried to Balance Sheet				
101 3 4					
		£46 16 10	£152 7 0		£46 16 10
£152 7 0					

SPECIAL LECTURES FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
— — —		— — —	— — —		— — —
17 10 9	To Dividends on Investment	24 11 3	25 0 0	By Honorarium	
10 8 0	„ Income Tax recovered	9 10 11	23 0 11	„ Lecture Expenses	1 14 4
13 7	„ Interest on Deposit	4 11		„ Miscellaneous Expenses	
	„ Balance, being Excess of Expenditure over Income, carried to Balance Sheet			„ Balance, being Excess of Income over Expenditure, carried to Balance Sheet	22 13 9
21 8 7					
£50 0 11		£34 7 1	£50 0 11		£34 7 1

Income and Expenditure Accounts of other Funds for the Year ended 31st December, 1949.

THE FARADAY LECTURE FUND.

1948	Income.	1949	1948	Expenditure.	1949
£ s. d.		£ s. d.	£ s. d.		£ s. d.
7 4 4	To Dividends on Investment	7 17 1	— — —	By Miscellaneous Expenses	12 9
5 16 5	„ Income Tax recovered	5 19 0		„ Balance, being Excess of Income over Expenditure, carried to Balance Sheet	15 5 8
0 0	„ Interest on Deposit	1 11	13 7 7		
£13 7 7		£13 17 0	£13 7 7		£13 17 0

THE TILDEN LECTURE FUND.

1948	Income.	1949	1948	Expenditure.	1949
£ s. d.		£ s. d.	£ s. d.		£ s. d.
41 13 4	To Dividends on Investments	27 3 0	15 15 0	By Honoraria	31 10 0
27 0 10	„ Income Tax recovered	27 11 1	6 11 3	„ Lecture Expenses	36 9 4
3 0	„ Interest on Deposit	3 0	— — —	„ Transfer to Publications Account, for cost of publication of Lectures	25 4 0
— — —	„ Balance, being Excess of Expenditure over Income, carried to Balance Sheet	31 11 9	— — —	„ Miscellaneous Expenses	3 4 10
			48 0 0	„ Balance, being Excess of Income over Expenditure, carried to Balance Sheet	— — —
£69 4 2		£90 9 1	£69 4 2		£90 9 1

CENTENARY FUND.

1948	Income.	1949	1948	Expenditure.	1949
£ s. d.		£ s. d.	£ s. d.		£ s. d.
173 0 0	To Dividends on Investments	240 10 0	163 6 9	By Expenses of Lecturers & Delegates	227 10 11
14 6 0	„ Income Tax recovered	206 17 8	4 8 0	„ Miscellaneous Expenses	17 7 4
			61 17 11	„ Balance, being Excess of Income over Expenditure, carried to Balance Sheet	67 9 9
£239 6 8		£447 7 8	£239 6 8		£447 7 8

THE ROBERT JOHN FLINTOFF TRUST.

1948	Income.	1949	1948	Expenditure.	1949
£ s. d.		£ s. d.	£ s. d.		£ s. d.
— — —	To Interest	3 17 9	— — —	By Balance, being Excess of Income over Expenditure, carried to Balance Sheet	3 17 9
		£3 17 9			£3 17 9

THE CHEMICAL SOCIETY.—BALANCE SHEETS, 31st December, 1949.

GENERAL PURPOSES.

1948 £ s. d.	1948 £ s. d.	*Liabilities.*	1949 £ s. d.	1949 £ s. d.
		To Sundry Creditors:		
4650 10 1		Fellowship Subscriptions in advance	9602 7 8	
2330 9 9		Publications sold in advance	3221 12 11	
8115 2 1		Printing and other Expenses	10,558 13 7	
	15,096 1 1			23,382 14 2
28,874 10 0		„ Excess of Assets over Liabilities as per last Balance Sheet	24,080 17 6	
246 8 4		*Add* Life Composition Fees (£69 13s. 0d.) (two-thirds)	46 10 0	
1,802 19 10		*Add* net Profit on change of investments	... ...	
30,123 6 2			24,127 7 4	
1,033 6 10		*Deduct* Excess of Expenditure over Income for year	111 6 5	
	24,090 17 4			24,016 2 11
	£39,186 19 5			£47,408 17 1

1948 £ s. d.	*Assets.*	1949 £ s. d.
28,736 17 6	By Investments as per Schedule (cost or value when acquired)	23,996 13 9
7,061 10 7	„ Sundry Debtors	10,232 4 8
300 0 0	„ Subscriptions in Arrear estimated to realise	300 0 0
1,441 10 2	„ Stock of Paper (Journal, Annual Reports, and Quarterly Reviews)...	1,414 5 7
1,647 1 5	„ Cash at Bank and in hand	6,373 10 8
£39,186 19 5		£47,408 17 1

THE CHEMICAL SOCIETY. BALANCE SHEETS, 31ST DECEMBER, 1949.

PUBLICATIONS FUND.

1948	*Liabilities.*	1949	1948	*Assets.*	1949
£ s. d.		£ s. d.	£ s. d.		£ s. d.
107 4 0	To Sundry Creditors	— — —	9,979 10 7	By Investments as per Schedule (cost or value when acquired)	10,970 19 7
8,708 10 6	„ Excess of Assets over Liabilities as per last Balance Sheet	9,978 19 7	107 4 0	„ Cash at Bank	— — —
270 9 1	*Add* net profit on change of Investments	— — —			
— — —	*Add* Legacy—W. H. Perkin	1,000 0 0			
£10,086 3 7		£10,978 19 7	£10,086 3 7		£10,970 19 7

SPECIAL RESERVE FUND.

£ s. d.	£ s. d.		£ s. d.	£ s. d.	£ s. d.		£ s. d.	£ s. d.
	2,150 3 7	To Sundry Creditors		1900 0 0	14,558 7 0	By Investments as per Schedule (cost or value when acquired)	6458 7 0	
		„ Reserve for Publications as per last Balance Sheet	9185 0 7		1,811 15 9	„ Cash at Bank and on Deposit in London Savings Bank	444 16 1	
11,185 0 7								
2,100 0 0		Deduct Amount transferred to Publications Account	9000 0 0					
	3,085 0 7			85 0 7				
1,560 0 3		„ Reserve for Library Books and Binding as per last Balance Sheet	1300 17 8					
60 2 7		Deduct Amount transferred to Library Account for Books	— — —					
	1,500 17 8			1300 17 8				
	3,200 0 0	„ Reserve for Research Fund as per last Balance Sheet		1250 0 0				
	225 0 0	„ Reserve for Building Fund		625 0 0				
1,848 7 0		„ Excess of Income over Expenditure brought forward	1630 1 11					
— — —		*Add* Profit on Sale of Investments ...	51 19 0					
186 18 1		*Add* Excess of Income over Expenditure for year	431 5 5					
2,034 5 1			£123 6 10					
404 5 5		*Deduct* Net Loss on change of Investments	— — —					
	1,630 1 11			7133 6 10				
	£18,370 3 9			£8908 5 1	£16,370 2 9		£6908 5 1	

THE CHEMICAL SOCIETY. BALANCE SHEETS, 31ST DECEMBER, 1949.

RESEARCH FUND.

1948 £ s. d.	£ s. d.	*Liabilities.*	1949 £ s. d.	£ s. d.
	535 13 10	To Sundry Creditors		742 0 9
		„ Excess of Assets over Liabilities as per last Balance Sheet	20,689 8 10	
20,727 3 4		*Add* net Profit on change of Investments		
141 7 10				
20,868 11 2			20,689 8 10	
179 2 4		*Deduct* Excess of Expenditure over Income for year	111 13 0	
	20,689 8 10			20,577 15 10
	£21,225 2 8			£21,320 16 7

1948 £ s. d.	*Assets.*	1949 £ s. d.
19,493 17 5	By Investments as per Schedule (cost or value when acquired)	19,492 17 5
1,722 1 3	„ Cash at Bank (including Deposit) and on deposit in Post Office Savings Bank	1,827 19 4
£21,216 2 8		£21,320 16 7

SPECIAL PUBLICATIONS FUND.

£ s. d.	£ s. d.		£ s. d.	£ s. d.
	3 5 3	To Sundry Creditors		65 7 3
		„ Excess of Assets over Liabilities as per last Balance Sheet	3307 5 11	
3116 1 11		*Add* Net Profit on change of Investments		
411 19 10				
3528 1 9			3307 5 11	
320 15 10		*Deduct* Excess of Expenditure over Income for year	382 3 3	
	3207 5 11			2925 4 8
	£3210 9 2			£2990 11 11

£ s. d.	*Assets.*	£ s. d.
33 9 10	By Sundry Debtors	39 11 6
2011 19 10	„ Investments as per Schedule (cost or value when acquired)	2011 19 10
1174 19 6	„ Cash at Bank and on deposit in the Post Office Savings Bank and London Savings Bank	939 0 9
£3210 9 2		£2990 11 11

STAFF PENSIONS FUND.

£ s. d.	£ s. d.		£ s. d.	£ s. d.
	— — —	To Sundry Creditors		6 14 2
		„ Excess of Assets over Liabilities as per last Balance Sheet	5058 15 1	
5063 6 7		*Add* Profit on sale of Investments	160 6 6	
— — —				
5063 6 7			5219 3 7	
81 16 3		*Deduct* Net Loss on change of Investments	— — —	
722 15 3		*Deduct* Excess of Expenditure over Income for year	527 7 10	
	5058 15 1			4651 15 9
	£5058 15 1			£4658 10 0

£ s. d.	*Assets.*	£ s. d.
— — —	By Sundry Debtors	500 0 0
4163 17 6	„ Investments as per Schedule (cost or value when acquired)	3736 6 0
892 17 7	„ Cash at Bank and on deposit in the Post Office Savings Bank	662 4 0
£5058 15 1		£4658 10 0

THE EDWARD FRANK HARRISON MEMORIAL TRUST FUND.

1948			*Liabilities.*	1949			1948			*Assets.*	1949		
£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
—	—	—	To Sundry Creditors										
			„ Excess of Assets over Liabilities as per last Balance Sheet										
1040	3	1				2	6	10					
—	—	—	*Add* Excess of Income over Expenditure for year	1146	10	9							
1040	3	1		44	10	0							
			Deduct Excess of Expenditure over Income for year	1191	9	9							
101	3	4		—	—	—							
		1146	10	9		1191	9	9					
		£1146	10	9		£1193	16	7	£1146	10	9	£1193	16	7

SPECIAL LECTURES FUND.

£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
—	—	—	To Sundry Creditors										
			„ Excess of Assets over Liabilities as per last Balance Sheet										
1239	4	6				1	14	4	1502	5	0	1515	5	0
—	—	—	*Add* Excess of Income over Expenditure for year	1582	0	11							
344	5	0		32	13	9							
—	—	—	*Add* Net Profit on change of Investment ...	—	—	—							
1583	9	6		1614	13	8							
			Deduct Excess of Expenditure over Income for year	—	—	—							
21	8	7											
		1562	0	11		1614	13	8						
		£1562	0	11		£1616	8	0	£1562	0	11	£1616	8	0

THE FARADAY LECTURE FUND.

£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
—	—	—	To Sundry Creditors										
			„ Excess of Assets over Liabilities as per last Balance Sheet										
						13	9						
457	6	2		470	13	9							
			Add Excess of Income over Expenditure for year										
13	7	7		13	3	3							
		470	13	9		483	17	0						
		£470	13	9		£484	10	9	£470	13	9	£484	10	9

THE CHEMICAL SOCIETY. BALANCE SHEETS, 31ST DECEMBER, 1949.

THE TILDEN LECTURE FUND.

1948 £ s. d.	£ s. d.	*Liabilities.*	£ s. d.	£ s. d.	1949 £ s. d.
	25 4 9	To Sundry Creditors		29 8 10	
1966 2 3		„ Excess of Assets over Liabilities as per last Balance Sheet	2014 9 3		
48 0 0		*Add* Excess of Income over Expenditure for year	— — —		
2014 2 3			2014 9 3		
— — —		*Deduct* Excess of Expenditure over Income for year	21 11 2		
	2014 9 3			1992 11 1	
	£2039 6 3			£2010 19 11	

1948 £ s. d.	*Assets.*	1949 £ s. d.
1878 14 10	By Investments as per Schedule (cost or value when acquired)	1878 14 10
160 11 8	„ Cash at Bank (including Deposit)	132 5 1
£2039 6 3		£2010 19 11

CENTENARY FUND.

£ s. d.	£ s. d.		d.	£ s. d.	£ s. d.	£ s. d.		£ s. d.
	— — —	To Sundry Creditors			77 15 10	1,197 9 9	By Sundry Debtors	— — —
		„ Capital Account :				15,686 3 6	„ Investments as per Schedule (cost or value when acquired)	17,160 3 6
11,797 7 1		Contributions under Deeds and Donations brought forward	14,624 9 4			767 14 4	„ Cash at Bank	132 10 5
3,190 16 11		*Add* Contributions under Deeds and Donations for year	2,707 17 6					
14,988 4 0			17,332 6 9					
801 16 8		*Deduct* Net Loss on change of Investments	— — —					
	14,624 9 4			17,332 6 9				
61 17 11		„ Excess of Income over Expenditure for year	57 0 2					
28 15 10		*Deduct* Excess of Expenditure over Income brought forward	— — —					
— — —		*Add* Excess of Income over Expenditure brought forward	33 2 1					
	33 2 1			190 11 3				
	£14,657 11 5			£17,530 13 9		£14,657 11 5		£17,530 13 9

THE ROBERT JOHN FLINTOFF TRUST.

£ s. d.	£ s. d.		£ s. d.	£ s. d.		£ s. d.
— — —		To Cash received from Executors	1000 0 0	— — —	By Investments as per Schedule (cost or value when acquired)	1000 0 0
— — —		*Add* Excess of Income over Expenditure for year	3 17 2	— — —	„ Cash at Bank	3 17 2
			£1003 17 2			£1003 17 2

SCHEDULE OF INVESTMENTS.

GENERAL PURPOSES.

Nominal Details.	*Cost or Value when Acquired.* £ s. d.	*Market Value 31st December, 1949.* £ s. d.
£1450 15s. 0d. 3½% Conversion Loan, 1961, or after	1084 13 9	2261 2 11
£3400 2s. 6d. 3% Funding Loan, 1959/69	3429 11 5	2535 17 7
£3400 14s. 9d. 3% Savings Bonds, 1960/70	3418 11 0	2326 14 2
£2000 3% Savings Bonds, 1965/75	2006 4 5	1606 0 0
£4747 4s. 8d. 3% British Transport Guaranteed Stock, 1978/88 ...	5704 9 8	4272 10 1
£3546 1s. 4d. 3% British Electricity Guaranteed Stock, 1968/73 ...	3549 4 5	2432 10 7
£1300 2½% Defence Bonds	1300 0 0	1300 0 0
£3400 2½% Bristol Corporation Debenture Stock, 1967	3070 2 0	2304 0 0
£1540 2½% London County Consolidated Stock, 1954/59	1630 2 6	1596 10 0
£2000 2½% London County Consolidated Stock, 1962/67	2032 10 0	2010 0 0
£2000 3% Commonwealth of Australia Registered Stock, 1964/66 ...	2009 7 6	2412 10 0
£A3170 4% Commonwealth of Australia Treasury Bonds, 1961 ...	1633 13 0	1765 8 3
£A530 4% Commonwealth of Australia Treasury Bonds, 1961 ...	719 5 7	678 6 0
	£18,096 13 9	£27,500 9 7

PUBLICATIONS FUND.

£2040 12s. 0d. 3½% Conversion Loan, 1961, or after	1806 16 4	2133 6 8
£1000 3% Savings Bonds, 1955/65	1000 0 0	991 6 0
£2361 1s. 11d. 3% Savings Bonds, 1960/70	2276 1 11	2190 8 9
£2175 13s. 4d. 3% British Transport Guaranteed Stock, 1978/88 ...	1929 1 4	1956 2 0
£2000 3% British Electricity Guaranteed Stock, 1968/73	2002 10 0	1863 15 0
£1200 3% Commonwealth of Australia Registered Stock, 1964/66 ...	1204 10 0	1158 0 0
£981 13s. 0d. 3% Southern Rhodesia Stock, 1971/73	1060 0 0	985 9 6
	£10,978 19 7	£11,330 6 7

SPECIAL RESERVE FUND.

£1300 2½% Defence Bonds	1300 0 0	1300 0 0
£1500 3% Savings Bonds, 1955/65	1500 0 0	1496 17 6
£2483 10s. 0d. 3% Liverpool Corporation Stock, 1955/58	2647 2 0	2804 11 10
£3000 2½% Funding Loan, 1956/61	3011 5 0	2970 0 0
	£8458 7 0	£8561 9 4

RESEARCH FUND.

£4177 10s. 1d. 3½% Conversion Loan, 1961, or after	3521 16 3	3937 3 9
£800 Defence Bonds, 4th issue	800 0 0	800 0 0
£4000 3% Savings Bonds, 1960/70	4000 0 0	3573 0 0
£3785 2s. 1d. 3% British Transport Guaranteed Stock, 1978/88 ...	3567 19 5	3379 11 11
£3719 6s. 2d. 3% British Electricity Guaranteed Stock, 1968/73 ...	3734 1 2	2540 7 10
£4000 3% Commonwealth of Australia Registered Stock, 1964/66 ...	4075 0 0	3900 0 0
	£19,498 17 5	£18,063 3 6

ROBERT JOHN FLINTOFF TRUST.

£335 2s. 9d. 3½% Conversion Loan, 1961, or after	300 0 0	431 14 5
£645 13s. 4d. 3% British Transport Guaranteed Stock, 1978/88 ...	600 0 0	491 7 5
	£900 0 0	£923 1 10

SPECIAL PUBLICATIONS FUND.

Nominal Details.	*Cost or Value when Acquired.* £ s. d.	*Market Value 31st December, 1949.* £ s. d.
£718 5s. 10d. 3½% Conversion Loan, 1961, or after	541 3 4	672 10 3
£746 1s. 0d. 3% British Transport Guaranteed Stock, 1978/88 ...	719 16 9	671 8 13
£700 3% British Electricity Guaranteed Stock, 1968/73	750 18 9	713 18 1
	£2011 19 10	£2057 17 5

STAFF PENSIONS FUND.

£114 1s. 11d. 3½% Conversion Loan, 1961, or after	86 2 1	107 5 0
£150 3½% National War Bonds, 1951/53	150 0 0	148 10 7
£170 3% Savings Bonds, 1955/65	170 0 0	170 0 0
£618 3% Savings Bonds, 1960/70	618 2 9	618 10 0
£818 2s. 7d. 2½% Funding Loan, 1956/61	2900 0 0	2500 0 0
£2500 2½% Defence Bonds	£3726 4 0	£3786 15 1

THE EDWARD FRANK HARRISON MEMORIAL TRUST FUND.

£61 18s. 8d. 3½% Conversion Loan, 1961, or after	60 1 5	58 1 4
£1489 10s. 6d. 3% British Transport Guaranteed Stock, 1978/88 ...	1051 6 6	1340 11 8
	£1101 7 11	£1398 13 0

SPECIAL LECTURES FUND.

£1501 18s. 8d. 3% British Transport Guaranteed Stock, 1978/88 ...	£1510 8 0	£1400 3 0

THE FARADAY LECTURE FUND.

£441 1s. 11d. 3½% Conversion Loan, 1961, or after	£439 4 0	£434 12 7

THE TILDEN LECTURE FUND.

£419 4s. 10d. 3% Funding Loan, 1959/69	396 12 10	406 15 3
186 National Provincial Bank Shares £5 each, £1 paid "B"	670 15 0	467 6 6
£681 10s. 1d. 3% British Transport Guaranteed Stock, 1978/88 ...	625 2 0	413 16 2
£200 3% Metropolitan Water Board (East Water Works) Deb. Stock	188 2 0	177 2 0
	£1870 14 10	£1464 16 11

CENTENARY FUND.

£5477 12s. 11d. 3% Savings Bonds, 1955/65	5491 11 10	5454 0 4
£3000 3% Savings Bonds, 1960/70	3154 7 6	2451 17 6
£1970 1s. 0d. 3% New Zealand Stock, 1973/77	2000 0 0	1834 15 2
£2705 12s. 7d. 2½% Savings Bonds, 1964/67	2650 0 0	2230 0 10
£3000 3% British Electricity Guaranteed Stock, 1968/73	3499 6 9	2379 13 6
£3279 12s. 0d. 3% British Transport Guaranteed Stock, 1978/88 ...	3287 7 9	2041 15 8
£A1000 4% Commonwealth of Australia Treasury Bonds, 1961 ...	1025 7 6	1000 5 11
	£17,199 3 4	£10,014 6 11

W. A. AKERS, *Treasurer.*

We have examined the above Balance Sheets and accompanying Income and Expenditure Accounts with the Books and Vouchers of the Society, and certify them to be in accordance therewith. We have also verified the Balances at the Bankers and Investments. An interim payment of £1700 on the Cowley-Morgan Memorial Fund has been received from the Public Trustee and is not included in the Accounts this year.

PEMBERTON CHEQUE HOUSE,
BUCKLERSBURY, E.C.2.
MARCH 10TH, 1950.

W. P. KEEN & CO.
Chartered Accountants.

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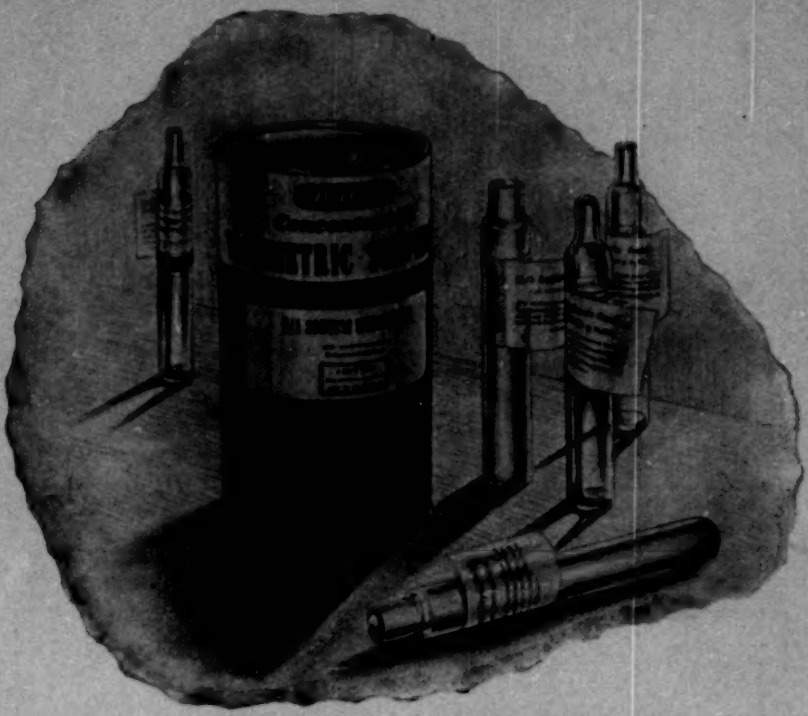

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